WHO technical meeting on sleep and health

Bonn Germany, 22-24 January 2004

World Health Organization Regional Office for Europe
European Centre for Environment and Health
Bonn Office

ABSTRACT

Twenty-one world experts on sleep medicine and epidemiologists met to review the effects on health of disturbed sleep. Invited experts reviewed the state of the art in sleep parameters, sleep medicine and, long-term effects on health of disturbed sleep in order to define a position on the secondary and long-term effects of noise on sleep for adults, children and other risk groups. This report gives definitions of normal sleep, of indicators of disturbance (arousals, awakenings, sleep deficiency and fragmentation); it describes the main sleep pathologies and disorders and recommends that when evaluating the health impact of chronic long-term sleep disturbance caused by noise exposure, a useful model is the health impact of chronic insomnia.

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Introduction

We spend almost a third of our life sleeping. Good quality sleep is essential for good health and well-being. However, lifestyle and environmental factors are increasingly causing difficulties in sleeping. Sleep disturbance is frequently considered the most serious consequence of environmental noise.

The WHO European Centre for Environment and Health expanded its work on sleep disturbance (focusing on the health consequences of poor sleep as well as on noise disturbance itself) in order to define a position on the secondary and long-term effects of noise on sleep for adults, children and other risk groups. 21 international specialists on sleep, including psychiatrists and psychologists, gathered in Bonn from 22 to 24 January 2004.

This document describes the meeting discussion and presents the conclusions and recommendations. Dr Christopher Drake reviewed the conclusions and recommendations.

A note on sleep

Sleep is a basic human need and is essential for good health, good quality of life and performing well during the day. Several indicators can be used to describe sleep disturbance or sleep disorders. These indicators are:

1) Sleep latency
2) Number and duration of nocturnal awakenings;
3) The total sleep time
4) Modifications in amount and proper rhythms of particular sleep stages such as slow wave sleep (SWS, or stages 3 and 4);
5) Rapid Eye Movement sleep (REM sleep), together with modifications in the autonomic functions (heart rate, blood pressure, vasoconstriction and respiratory rate);
6) Repetitive nights of sleep disruption among one week or one month.

Self-reported sleep can also be used as an indicator: it is considered the least reliable objectively but perceived as the most important by the individual.

Health effects of not sleeping

The main effects of sleep deprivation include **physical effects** (sleepiness, fatigue, hypertension) **cognitive impairment** (deterioration of performance, attention and motivation; diminishment of mental concentration and intellectual capacity and increase of the likelihood of accidents at work and during driving) and **mental health complications**. Inadequate rest impairs the ability to think, to handle stress, to maintain a healthy immune system, and to moderate emotions. Maintained total sleep deprivation is fatal in some animal species.

The day after a night of abnormal or poor sleep is, whatever the cause, a disturbed day. People can fall asleep at work, at school or when driving; feel tired; have concentration and vigilance detriments; have memory blanks; irritability; frustration; and have a higher probability of accidents or injury (WHO, 1998).

Scope of the meeting

The main purpose of this meeting was to identify the current links between sleep disturbance (under all its modalities) and health status of adults, children and risk groups (shift workers, elderly, insomniacs), both on a long term and short term basis.

The following figure illustrates the reasoning and logic behind the meeting preparation and the starting point for the writing of the meeting background papers.
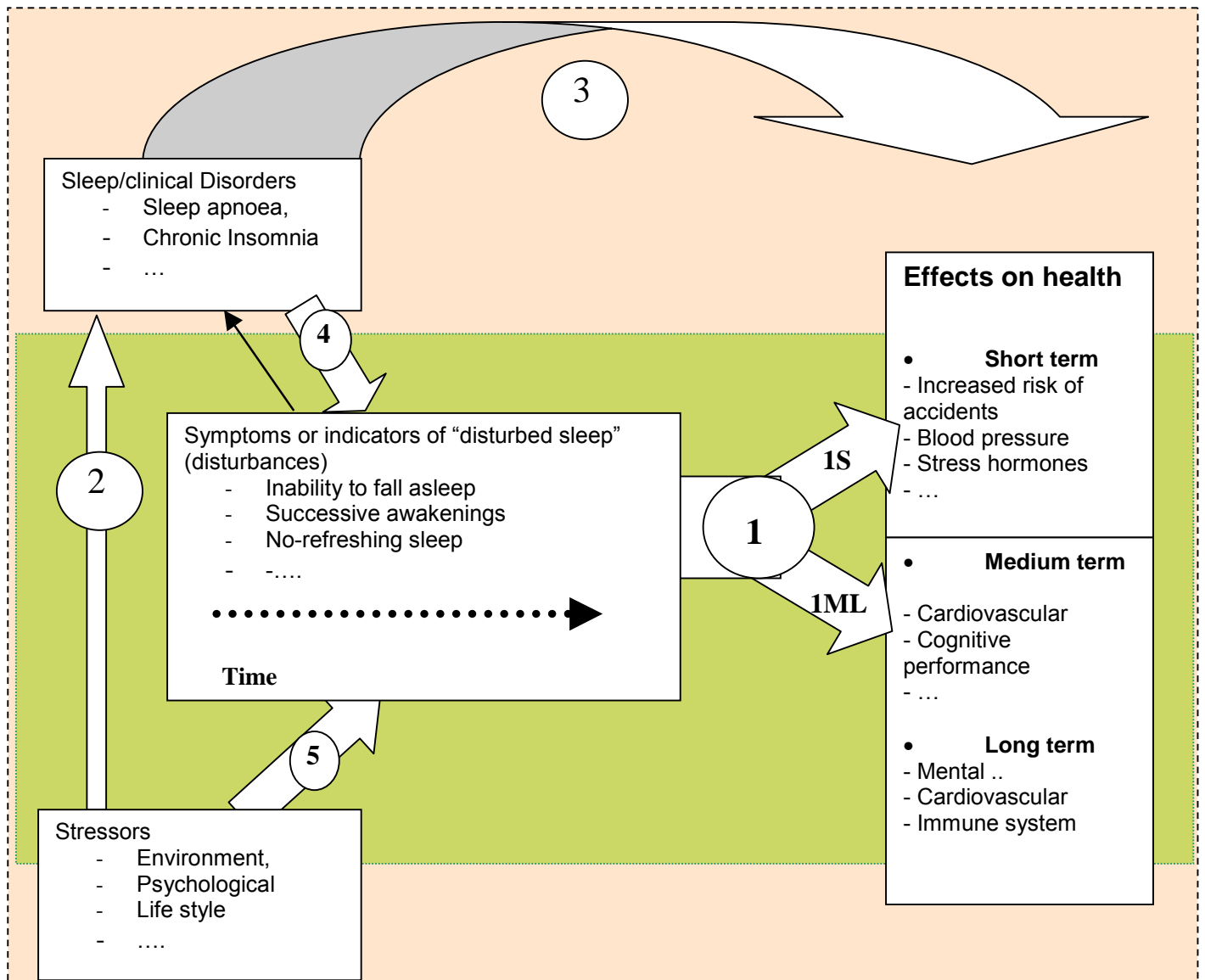
Figure 1 – Scope of the meeting

Main themes for the technical papers of the meeting   Results

(1) - Most unknown ; **(2)** - Little known ; **(3)** Important body of knowledge ; **(4)** Important body of knowledge ; **(5)** Important body of knowledge

With three groups of population in mind (adults, children and specific risk groups) the meeting reviewed:

1.Sleep physiology: what is a "normal" sleep? What are the various types of sleep disturbances? What kind of indicators are used to describe each of these types of disturbances? (Awakenings, arousals, body movements, changes of sleep stages, cortisol secretion etc.);

2. Are there specific sleep disturbances that are of special relevance for some "risk groups", and why? (This will cover children, elderly, shift workers, etc.).

3. The various health end points than can be linked to sleep disturbances.

Summary of the meeting discussion

Dr G. Klein welcomed the participants on behalf of Dr. M. Danzon, Regional Director of the WHO Regional Office for Europe. He introduced the WHO Regional Office for Europe and the work on noise and health and provided some key figures for noise and sleep in Germany.

Mr. Bonnefoy explained the background and the goals of the meeting and how it escapes the traditional work of the WHO noise and health unit and how the results will be used for the unit's future actions.

Mrs. C. Rodrigues presented the meeting objectives and provided some methodological guidance in order to optimize the work during the meeting.

In summary, the group was challenged to provide a definition of a normal sleep, of arousals and their significance, sleep deficiency, sleep fragmentation, and, awakenings, using scientifically based and accepted evidence and to answer some central questions:

- Can we use the knowledge gained in evaluating the impact on health of a sleep pathology to assess the impact on health of sleep disturbed by noise? If yes which pathology would be best suited and what would be the limits to such an assumption? This would help to translate the knowledge gained by clinicians to support advice to Member States on their noise and health policies.

- Can we list and describe the causes of sleep disturbances, the sleep changes and the health effects (figure 2) having for each arrow the evidence, the gaps in knowledge, public health significance and the consideration of confounding factors?
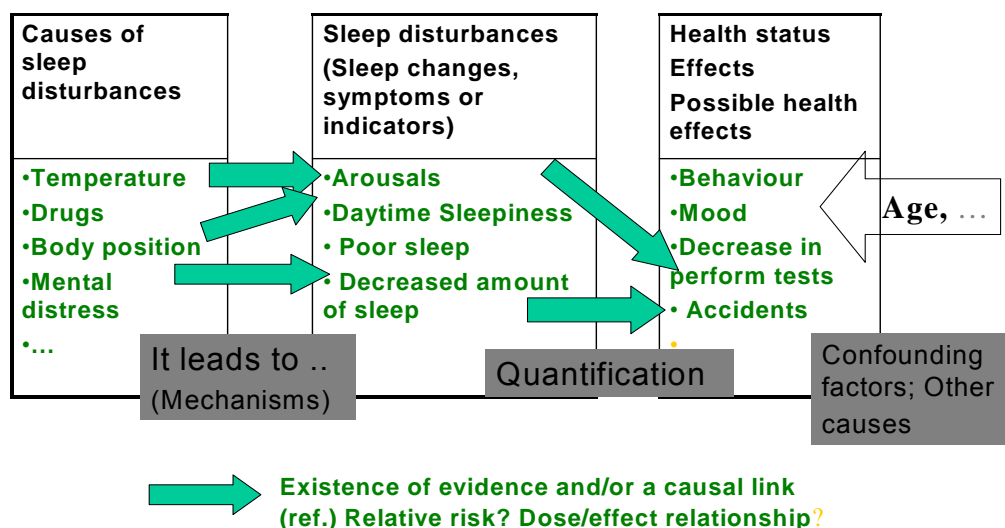
Figure 2 – Illustration of some points proposed for discussion

The invited experts presented seven papers, followed by a short discussion within the whole group. More detailed in-depth discussions about these presentations took place during working groups on adults and children.

The seven papers are attached as annex 2. They were dealing with the following topics :

1. Adult's sleep physiology; sleep quality and indicators of disturbed sleep. Main causes of sleep disturbances on adults - Alain Muzet

2. Sleep characteristics and sleep deprivation in infants, children and adolescents - André Kahn

3. Sleep disorders in adults; biological mechanisms through which sleep disorders affect the health of adults. Identification of environmental factors leading to clinical sleep disorders - Michel M. Billiard

4. Sleep disorders in children, mechanisms through which sleep disorders affect the health of children - Alfred Wiater

5. Medium and long term effects of sleep disturbance (by disorders and/or by stressors) on the health of adults - Sonja Nevsimalova

6. Medium and long term effects of disturbed sleep on the health of children - Oliviero Bruni

7. Sleep - gender, age, stress, work hours - Torbjörn Åkerstedt

"Adult's sleep physiology; sleep quality and indicators of disturbed sleep. Main causes of sleep disturbances on adults led by Prof. Alain Muzet

In order to answer questions about the effects of sleep disturbances on health an agreement on definitions of sleep patterns and different types of sleep disturbances is essential. The paper dealt with "normal" sleep physiology, the factors that could interfere with the physiologic processes and the immediate effects observed when sleep is disturbed.

The author suggested that very little is known on why we sleep, a little more is known on how we sleep. He then introduced what could be understood as a "normal" sleep.

To some degree, sleep disturbance may be quantified by EEG measures, autonomic variables, motor and hormonal responses. The normality of sleep can be influenced by stages of sleep, individual factors, and context factors. We can measure it in adults with **subjective** complaints (poor sleep quality, daytime fatigue, changes in mood, ..) and **behavioural** changes the next day (daytime drowsiness, performance decrement, drug consumption, …).

There is no habituation of the cardiovascular responses to noise. Each noise stress on the human body is associated with a cardiovascular response that is composed of a vasoconstriction of peripheral circulatory system and an increase of blood pressure even if the sleep itself is not affected.

The questions raised at this session were used as the basis for defining the working groups' terms of reference. The main points are the following:

- Sleep should be defined according to age and gender;

- Attention has to be paid to pharmacological effects;(related to sleeping drugs). There are a number of factors that influence sleep quality and quantity;

- Arousals and interactions with sleep stages seem to be important,

- Sleep stages are important. What the brain is performing during the different sleep phases when it gets interrupted is important!

- Not only awakenings are important! Autonomic responses/repeated cardio vascular responses have no habituation to noise.

- The REM sleep has a tissue-repairing function, both macrostructure of sleep and microstructure (cortical arousals, sub cortical arousals) are important.

- The cardiovascular responses are independent from sleep disturbance! A person may sleep with a relatively high noise level, nevertheless he/she continues to have autonomic responses. Similarly what happens at the level of the heart does not affect the sleep. Cortical responses are always related with cardio vascular responses.

- During sleep the cortex is switched off.

- For decision makers it is important to provide guidelines and references easy to transfer to legislation.

- How to evaluate sleep quality and sleep quantity? Is sleep satisfaction a good measurement?

- Is sleep a fragile state or is it because of the sleep function that we are more fragile?

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Most of these questions were answered in the working groups.

Sleep characteristics and sleep deprivation in infants, children and adolescents – led by Prof André Kahn.

A normal childhood is crucial to a healthy adult life. Children's sleep patterns are very different from adults, deserving therefore special attention. The existing knowledge of health effects of sleep disturbance on children is not very large.

Prof André Kahn provided a review of a child's "normal" sleep, the factors that have an influence on it and the immediate effects observed when their sleep is disturbed. Sleep recording techniques, normal sleep characteristics, and some of the effects of sleep deprivation in children were described. The presentation focused then on normal sleep characteristics for foetuses, infants, children and adolescents, the short-term effects of sleep deprivation and on the effects of repeated sleep deprivation /co-morbidity.

Short-term effects of sleep deprivation in school-age children appear to be manifested by daytime fatigue only; medium-term effects have been associated with daytime sleepiness and behaviour problems. Attention-deficit/hyperactivity disorder has been suggested as a possible consequence of non-sleep among children. On the medical level the body of evidence is still poor.

Effects of repeated sleep deprivation in infants, children and adolescents are multifactorial and complex, but repeated or chronic sleep disruption in children could be pervasive, affecting the children's physical, mood and cognitive well being. Changes in sleep quantity and quality together with autonomic reactions are seen during exposure to ambient stressors during sleep, reflecting modifications within the brain of the sleeping child. It remains, however, to be determined what long-term effects pervasive ambient stressors have on the child's cognitive, mood and physical development.

One might predict that the effects of sleep deprivation on the child's sleep and health depend upon the stressor responsible for the deprivation or fragmentation of sleep, temporal aspects of the stressor, genetic predisposition, psychological responses to the stressor, and the nature as well as the duration of the evaluation.

All research on sleep and health in children needs to follow very strict ethical rules. This explains partly the lack of knowledge observed in some areas.

Important points raised at the discussion:

- The definition of the "normal child sleep" parameters is extremely important, they should be listed before starting to identify a disturbed sleep in order to be able at a further stage to identify its consequences.

- Repeated sleep deprivation or insomnia were discussed in detail. A child cannot accurately report about his/her sleep, so it is difficult to define sleep efficiency and to base further findings on this evaluation technique.

- Special attention has to be paid to the methods of evaluating the status of a child after a deprived night. Fatigue does not reflect equally in adults and children: a child can be hyperactive due to a disturbed sleep.

- We need indexes and indicators that measure sleep quality in children.

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- The different parts of the night, in children for example, play different roles. The growth hormone is released in the first part of the night and it does not happen in the second part of the night, but there is little data to show this.

- Are children less sensitive to noise?, It is true that a child can sleep with high noise levels. This faculty decreases with age. Most of the evidence is based on parents' reports as the main source of information and it is likely that the child did sometimes wake up but the parent did not notice it.

Sleep disorders in adults; biological mechanisms through which sleep disorders affect the health of adults. Identification of environmental factors leading to clinical sleep disorders led by Prof. Michel M. Billiard

There are several types of sleep disorders. Insomnia, sleep apnoea, and restless leg syndrome are some examples of clinical sleep disorders that can affect adults and interfere with normal functioning. These sleep disorders can contribute to medical or emotional problems. This is a field where a vast body of knowledge exists. For this meeting over-information was avoided and the paper reviewed and presented the main sleep disorders in adults and the health and well-being consequences of these diseases. It focused on sleep disorders that were considered interesting, in the expert's opinion, for discerning the health impacts of sleep that is occasionally or chronically disturbed by noise.

According to the Diagnostic and Statistical Manual of Mental Disorders there are four categories of sleep disorders, i) primary sleep disorders including dyssomnias, ii) parasomnias, iii) sleep disorders related to medical/psychiatric disorders including insomnia and hypersomnia; iv) and other sleep disorders including disorders due to a general medical condition or a substance- induced sleep disorder. The presentation concentrated on dyssomnias, parasomnias, medical/psychiatric sleep disorders, obstructive sleep apnea/hypopnea syndrome, narcolepsy-cataplexy, environmental sleep disorder and periodic limb movement disorder.

Primary insomnia is a dyssomnia and it has been shown that the pathophysiology of the disorder is considered to be based on the confluence of predisposing, precipitating and perpetuating factors. In a predisposed subject, noise may certainly act as a triggering factor. Narcolepsy-cataplexy is most often remarkable for sleep fragmentation. However, in contrast to the obstructive apnea/hypopnea syndrome there is no correlation between sleep fragmentation and excessive daytime sleepiness.

Moreover the pathophysiology of narcolepsy is based on an imbalance between acetylcholine and monoamines and on an impairment of the hypocretin system, which are not found in noise induced insomnia.

A polysomnographic feature of obstructive sleep apnea/hypopnea syndrome and upper airway resistance syndrome, consists in recurrent arousals and awakenings. Interestingly, most of subjects with these conditions do not complain of poor sleep, but of non-restorative sleep, fatigue and/or headache on morning awakening, and excessive daytime sleepiness. These clinical features are certainly an incentive to look for morning symptoms and excessive daytime sleepiness in subjects submitted to an abnormal level of noise.

Environmental sleep disorder has noise as one of its possible sources, possibly the most important one. Two issues have been emphasized. First, environmental disorder does not refer only to insomnia but also to excessive sleepiness, so that the possibility of excessive daytime sleepiness in subjects undergoing a noisy environment must be kept in mind. Second, vulnerability to either insomnia or hypersomnia, must be considered when reviewing the risks from environmental sleep disorder.

One of the polysomnographic features of periodic limb movement disorder is arousals and awakenings. However periodic limb movements do not seem to be the cause of arousals and awakenings. Even if noise disturbance manifests by arousals and awakenings the biological mechanisms that act on the basis of these disorders are different and in some cases due to chemical unbalances, or respiratory mechanisms, so the consequences will be different as well.

The symptoms of insomnia are very similar to the ones experienced by the people reporting noise sleep disturbance. But the single fact of having noise does not make everybody exposed insomniac. It is a very interesting finding but has to be analyzed with some caution. An insomniac is hyper-aroused, he is never sleepy.

Is there evidence that people suffering from insomnia have an increased mortality risk? Not really: there is a statistical association but we cannot say with the present state of knowledge that insomnia per se brings an increases risk of mortality. Some causality was found with hypnotic drugs taken when suffering from insomnia!

Misinterpretations and misperception of sleep is common among insomniac people, they affirm not having slept and when surveyed in a laboratory they actually sleep.

The insomniac subjects followed by Professor Billiard showed an increased body mass index, but obesity was not covered by the study.

Sleep disorders in children, mechanisms through which sleep disorders affect the health of children led by Dr Alfred Wiater

Healthy sleep is crucial for normal development and common sleep problems are seen in general paediatric practice. Children's sleep patterns are different from adults and so are their clinical sleep disorders. Nightmares, bedwetting, sleep walking are some examples of common sleep disorders experienced by children that can affect and compromise children's development. These sleep disorders can contribute to medical or emotional problems. The specific influence of noise on children's sleep should be examined in order to find appropriate measures for reduction.

Dr Wiater's presentation concentrated on the main sleep disorders that affect children's sleep and the main findings of a study carried out in Germany in 2000 by a group of paediatricians and child psychiatrists to evaluate sleep disorders and behaviour problems in 5-6 year-old and 9-10 year-old children.

Sleep disorders in children include intrinsic and extrinsic sleep disorders as well as parasomnias. Intrinsic sleep disorders comprise disorders such as the obstructive sleep apnea syndrome that can affect the health of children in the form of somatic disorders, e.g. cardiovascular or respiratory problems. Predominantly, extrinsic sleep disorders occur during childhood. Inadequate sleep hygiene, environmental sleep disorder, adjustment sleep disorder, limit-setting sleep disorder, and sleep-onset association disorder belong to this category. Extrinsic sleep disorders are strongly associated with behaviour problems such as hyperactivity or psychological symptoms.

Parasomnias, especially nightmares, can also be associated with psychological problems. Up to 35% of elementary school children of the Köln study presented sleep onset problems and 21% of this group have problems sleeping through the night. Usually, several sleep disorders can be diagnosed in one child. Environmental factors such as noise disturbances, can influence children's sleep. 15% of elementary school children complain about noise disturbances during sleep. The main source of noise is road traffic.

Sleep disorders in childhood are an important paediatric problem because of their influence on children's health and their strong correlation with behaviour problems. Parents often do not recognize their children's problems and disturbances. Educational efforts to make the children used to regular bedtimes and wake-up times from early childhood could be helpful for a normal sleep-wake-rhythm.

On the Cologne study the presence of a television set in the child's bedroom and reporting sleep problems by the child show strong association in this study. The children wake up earlier and go to bed later because they are watching TV. Some TV programmes in the early morning are specially designed for children.

Medium and long term effects of sleep disturbance (by disorders and/or by stressors) on the health of adults – led by Prof. r Sona Nevsimalova

The aim of the presentation was to examine the effects which the most frequent sleep disorders have on adults' health, knowing that at least 30% of the population suffer from some sort of sleep disturbance. The greatest impact on physical and mental health is seen in patients suffering from the sleep apnoea syndrome (neurocognitive, cardiovascular, social consequences and higher mortality), from insomnia (behavioural, psychiatric and medical consequences), and from narcolepsy and hypersomnia (neurobehavioral and personality changes, medical and social consequences). Patients suffering from the restless legs syndrome complain of neurobehavioral problems and lower quality of life, while the secondary forms of the disease are associated with other medical conditions. Parasomniacs are endangered by violent and injurious behaviour during attacks that can even involve the law.. Behavioural, cognitive and social consequences also affect patients with circadian rhythm disorders. Therefore, understanding the patient's health requires consideration of the state of the patient asleep and also awake.

The consequences of insomnia can be **behavioural** manifesting in poor performance at work, fatigue, memory difficulties, concentration problems, car accidents, **psychiatric problems** - depression, anxiety conditions, alcohol and other substance abuse, **medical** - cardiovascular, respiratory, renal, gastrointestinal, musculoskeletal disorders, impaired immune system function and an **increased** risk of mortality.

Is the sleep of pregnant women more susceptible to external stressors? We do not have evidence for this, but they are more prone to have some sleep disorders like restless legs syndrome, sleep disordered breathing or insomnia.

Insomnia increases the mortality risk, but in fact there are no accurate data, it's most probably linked with work-related accidents among sleep disturbed people. The "simple" fact of not sleeping does not lead to increased mortality associated with intrinsic health conditions.

Medium and long term effects of disturbed sleep on the health of children – led by Prof. Pr Oliviero Bruni

Sleep disorders during childhood represent an important children's health issue, these may affect cognitive development and learning during a critical brain growth period. The possible long-term effects (at the adult age) of chronically disturbed sleep during childhood were also considered.

Children with disturbed sleep presented cognitive dysfunction and behavioural disturbances, abnormal growth hormone release and increase of diastolic blood pressure, are all related to sleep fragmentation.

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Environmental noise at home at night could lead to sleep disruption without leading to behavioural awakenings through the alteration of sleep microstructure, in a similar manner as other sleep disturbing events such as respiratory disturbances

A major issue is that children who have experienced prolonged sleep disruption during a period traditionally associated with major brain growth and substantial acquisition of cognitive and intellectual capabilities may suffer from a partially irreversible damage, compromising their potential for academic achievement

In children, indicators of sleep disruption such as behavioral awakenings evaluated by actigraphs or sleep architecture abnormalities are not sufficient to evaluate correctly the consequences on growth, cognition and behaviour in children.

Professor Bruni suggested the respiratory disturbances during sleep as theoretical model to evaluate the effects of disturbed sleep in children because it manifests with arousals, and there is a lot of evidence on these disorders in children. This could raise controversy because the respiratory problems have other mechanisms associated that never occur when the sleep is disturbed by noise.

Sleep physiology, sleep quality and indicators of disturbed sleep on risk groups (elderly, shift workers; Main causes of sleep disturbances/disorders on specific risk groups and their known consequences- led by Prof Torbjörn Åkerstedt

Specific population groups linked by behaviour, life style, age, and gender, among other factors, can be at increased risk of having health problems from sleep disturbance. Stress due to work or family seems to be one of the major causes of disturbed sleep. The effect of stress on the risk of insomnia is well established, but reduced sleep in itself seems to yield the same physiological changes as stress. This suggests that several of the major civilization diseases in Europe and the US (diabetes, cardiovascular disease, burnout) could be mediated via disturbed sleep. This link clearly warrants longitudinal studies with interventions.

Shift workers constitute a group that suffers from disturbed sleep for most of their occupational life. The reason is the interference of work hours with the normal timing of sleep. This leads to an increased risk of accidents, directly due to excessive sleepiness, but also to cardiovascular and gastrointestinal disease, although it is not clear whether the latter effects are sleep related or due to circadian factors - or to a combination.

Data suggests that the risk of disturbed sleep increases with age but there also seems to be a recent stress related increase in sleep disturbances in young adults. The long term health consequences are not understood.

The relationship between gender and disturbed sleep is confusing. Females, as a rule complain more of sleep problems, but do not exhibit any objective indications of more disturbed sleep, at least not among otherwise healthy women. With increasing age the sleep of males deteriorates whereas that of women is relatively well upheld. Pregnancy, however, is a period of increased risk of disturbed sleep, whereas the menstrual cycle and menopause show less evidence of disturbed sleep. Clearly there is a great need of longitudinal research on gender and sleep and in particular on the possible health consequences around pregnancy.

Working Groups

On the second day the participants split into two working groups: one for children and one for adults. They examined the reviews presented the day before and tried to reach consensus on the report outline.

Working group 1 – children – rapporteur – Dr Alfred Wiater
Working group 2 – adults – rapporteur – Dr Damien Leger

The working groups tried to reach a consensus based on the meeting presentations and expert opinions about what is a "normal sleep" (depending upon age) what are "arousals" and the significance of arousals, including which are physiological and which can lead to health effects), how should the number of arousals be used as an indicator of disturbed sleep, "sleep deficiency", "Sleep fragmentation" and "awakenings".

The groups were challenged also to fill in a table (figure 2) providing for each arrow a quick review of the existing evidence and the identification of existing gaps in knowledge. For health effects, they were asked to explore the public health significance and to take into consideration all the confounding factors when describing them:

Both working groups were asked the following question:" To what extent can we assimilate the "sleep disturbances pattern" of various sleep diseases to those caused by external stressors and more specifically noise?"

The work of the working groups informed the conclusions and recommendations of this report.

Conclusions and recommendations

The following conclusions and recommendations have been agreed upon for children and adults:

Conclusions

1. Healthy sleep is necessary for children and adults' health and well-being. During normal sleep several physiological events take place such as cortical and sub cortical arousals and awakenings. The pathological increase of these physiological events could lead to sleep fragmentation and un-restorative sleep with several diurnal consequences.

2. The group evaluated the impact of disturbed sleep on the health of the general population. Children, pregnant women, peri menopausal women and elderly are major sub-divisions of the population that warrant special attention. There is some evidence that disturbed sleep among these groups may have more deleterious health effects than those observed among the general population.

3. Environmental stressors, such as noise, can alter the quality and the quantity of sleep. Nearly all findings relate to short-term sleep disturbances. The long-term effects of disturbed sleep due to noise need to be more carefully evaluated in prospective longitudinal studies.

For adults:

1. Normal sleep in an adult population can be characterized using specific methodologies:

   a) Questionnaires[1]: The "normally sleeping" population can be identified through positive response to questions such as the following:
      - Are you satisfied with your sleep?
      - Do you feel alert most of the day?
      - Do you feel refreshed by your sleep?
      - Sleep diaries/logs[2]

   b) Objective measures[3]:
      - Sleep duration could be defined by the number of minutes $\pm 2\sigma$ (to be provided by age groups and sex)
      - Number of arousals can be expressed in the number of hours $\pm 2\sigma$

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[1] References:
- Naresh M. Punjabi, MD, PhD; Karen Bandeen-Roche, PhD; Terry Young, PhD (2003);"Predictors of Objective Sleep Tendency in the General Population", [Electronic version] *SLEEP, Vol. 26, No. 6;*
- Joyce A. Walsleben PhD, Vishesh K. Kapur MD, Anne B. Newman MD, Eyal Shahar MD, Richard R.Bootzin PhD, Carl E. Rosenberg MD, George O'Connor MD, F. Javier Nieto MD (2003) "Sleep and Reported Daytime Sleepiness in Normal Subjects: The Sleep Heart Health Study"; [Electronic version] *Journal SLEEP, paper accepted for publication not published at present date;*

[2] Reference:
- Naomi Breslau; Thomas Roth; Leon Rosenthal; Patricia Andreski (Oct. 1997); "Daytime sleepiness: An epidemiological study of young adults"; [Electronic version] *American Journal of Public Health; 87, 10; ABI/INFORM Global*

[3] References:
- *Weissman et al. (1997);* General Hospital Psychiatry 19 (245 250);
- Ford kamarow (1989) *Jama 262, 1479-1484;*
- Breslav at al. (1996) Biological psychiatry

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- Sleep latency is the number of minutes ± 2σ (to be provided by age groups and sex)
- Sleep efficiency ≥ 85% (to be provided by age groups and sex)
- Number of awakenings

c) In addition the following two parameters have sometimes been considered. It should be noted that they do not reflect objective measurements:
- Actigraphic measures (i.e. sleep latency, sleep efficiency, total sleep time)
- Awakenings with behavioural response (e.g. button press)

2. The possible health consequences of chronic insomnia are becoming well documented[4]:

   a) higher risk of mortality (secondary to another psychiatric or somatic disorders)
   b) higher risk of depression (and other affective disorders) up to 5 times[5] more than general population
   c) increased somatic disorders: cardiovascular, gastrointestinal,
   d) twice as many medical visits, and hospitalizations (all causes included, four times more accidents than the general population)
   e) lower quality of life
   f) problems in family, work and school

3. Different epidemiological data suggests that about 30 to 35% of the general population complain about sleep problems and 9 to 11% suffer from chronic insomnia. These sleep problems have been related to:

   a) Co-morbid mental disorders (depression, anxiety, substance abuse)
   b) Primary insomnia
   c) Co-morbid medical disorders
   d) Restless legs syndrome
   e) Environmental sleep disorders, with noise being only one of the factors
   f) Hypnotic, stimulant, dependent sleep disorders

4. Noise is one of the most important known environmental stimulus disturbing sleep.

5. Noise is known to have a short-term impact on sleep. This impact can be assessed:
   a) Subjectively: sleep satisfaction, refreshment
   b) And objectively using psg, actigraphs based on mean values of total sleep time, sleep latency, index of arousal, sleep fragmentation.

6. It is scientifically established that sleep disturbances due to noise can have a short-term impact on daytime function by:
   a) Excessive daytime sleepiness
   b) Accidents[6] and drowsy driving
   c) Impaired neurobehavioral performance and mood

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[4] References:
- D. Leger et al, "Medical and Socio-Professional Impact of insomnia", SLEEP, Vol 25,No 6, pages 625- 629 , 2004
- D. Leger et al, "Les conséquences diurnes de l'insomnie: impact sur la qualité de vie » Rev Neurol (Paris) 2001 ; 157 :10, 1270-1278
- D. Leger, E. Levy, M. Paillard, "The direct costs of insomnia in France, sleep, Vol.22, Supplement 2, 1999 the direct costs of insomnia in France"

[5]Weissman et al. (1997); General Hospital Psychiatry 19 (245 250);
[6] R. Moore, D. Ormandy.

7. In the absence of experimental studies directly testing the long-term impact of noise on health, one way to assess the long-term consequences of noise is to adopt a model. Primary insomnia as defined by DSM-IV and DSM-III (Diagnostic and Statistical Manual of Mental Disorders) has been considered by the expert group as an acceptable model. The key criteria for defining insomnia are the following:

    a) At least three awakenings per night with difficulty getting back to sleep
    b) At least twice a week for at least one month

  This model would help us to estimate the possible impact of noise on health[7].

8. The impact of noise on sleep is heavily mediated by the psychological status of the individual. It can be argued that noise exposure can lead to the following sleep disturbances:
    a) Arousals and awakenings
    b) Sleep reduction
    c) Decreased sleep efficiency
    d) Increased sleep latency
    e) Subjectively decreased quality of sleep

In turn, these sleep disturbances, depending upon their severity, frequency of occurrence and chronicity may lead to:
    a) Decreased attention
    b) Accidents
    c) Reduced job performance and burn out
    d) Excessive daytime sleepiness
    e) Decreased quality of life

There are tentative associations between sleep disturbance and:
    a) Cardiovascular disorders, diabetes and obesity through mediation by cortisol excretion, decreased glucose assimilation and lipids
    b) Hypertension and possibly non-dipping of blood pressure during the night.

9. Based on the following accepted evidence:
    a) Noise, stress, and shift work can cause reduced sleep and fragmented sleep (TST, Sleep efficiency, microarousals).
    b) Sleep fragmentation can cause reduced glucose tolerance (dose-response is not well described)
    c) Reduced/fragmented sleep causes sleepiness and performance impairment in a dose-response fashion
    d) Reported poor sleep is associated with excess mortality, and cardiovascular disease. (Here we lack evidence of any causal mechanism but the metabolic changes can at least provide a likely explanation for the third outcome)[8]

It can be concluded that well established indicators of disturbed sleep are relevant to evaluating the impact of external stressors such as noise or stress. It is known that populations demonstrating "abnormal indicators" are associated with excess metabolic changes, mortality, and morbidity. Unfortunately there are no clear causal links, and one has to extrapolate based on the existing cause-effect relationship.

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[7] References:
- D. Leger et al, "Prevalence of insomnia in a survey of 12 778 adults in France" European sleep research society, 1999, pages 35-42
- D. Leger et al, "Evaluation of quality of life in severe and mild insomniacs compared with good sleepers", Psychosomatic medicine, No 63, 49-55
[8] Reference: Allen RP, Mortality associated with sleep duration and insomnia. Sleep Med 2002 ; 3 : 373-375

10. Wide variations exist in sensitivity among individuals to sounds during sleep. Consequently it is important that the clinician (and the WHO) not focus solely on the intensity of the noise, but additionally on its informational (cognitive or emotional) value.

For children

1. The group agreed upon the following set of definitions for the child population[9]:

a - **Normal sleep** is the sleep that satisfies a child's need according to age and culture and fulfils measurable parameters, somatic criteria, and psychological and behavioural criteria as described in literature

b - **Awakenings** – are a behavioural change where a child wakes up from sleep, opens the eyes and/or cries.

c - **Arousals** – sub cortical arousal is manifested by autonomic changes with no EEG changes; cortical arousal is manifested by concomitant autonomic and EEG changes.

d - **Sleep deficiency** – is characterized by too little sleep according to age, due to short or fragmented sleep.

e - **Sleep fragmentation** – is sleep with repeated arousals or awakenings that can lead to sleep deprivation and/or non-restorative sleep.

2. Children's sleep quality can be assessed through:

    a) Subjective measures
- Parental reports based on standardized questionnaires
- Paediatric Sleep Questionnaire (Chervin)
- Children Sleep Habits Scale (Owens)
- Sleep Disturbance Scale for Children (Bruni)
- Cognitive consequences (Sadeh)

    b) Indirect measures that evaluate day time consequences
- Child Behaviour Checklist (Achenbach)
- Conners Parent rating scales
- Paediatric Daytime Sleepiness scale (PDSS)[10]
- etc.

    c) Information may be obtained from actigraphic techniques;

    d) Objective measures mostly obtained through polysomnography:
- Arousals
- Awakenings
- Sleep deficiency
- CAP rate increase or modification

3. In children, noise exposure during night time leads to:
    a) Arousals (cortical/sub cortical)
    b) Sleep fragmentation
    c) Awakenings
    d) Sleep deficiency

4. These sleep disturbances, depending upon their severity, frequency of occurrence and chronicity as well as the age of the child may lead to:

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[9] References:
- *McNamara F, Lijowska AS and Thach BT. Spontaneous arousal activity in infants during NREM and REM sleep. Journal of Physiology, 538.1: 263–269, 2002;*
- Stores G. Crawford C. Arousal norms for children age 5-16 years based on home polysomnography. Technology & Health Care. 8(5):285-90, 2000;
- *Tasali EF, Mendelson WB, Spire JP, Kohrman MH. Arousal Index in 100 Children: normative data. Sleep, 24 (Suppl.): A208,2001*
- *Bruni O, Ferri R, Miano S, Verrillo E, Vittori E, Della Marca G, Farina B, Mennuni G. Sleep cyclic alternating pattern in normal school-age children. Clin Neurophysiol 2002; 113: 1806-1814*
- *Marcus CL. Sleep-disordered Breathing in Children. Am J Respir Crit Care Med 2001; 164: 163*

[10] Reference: Drake and al, 2003 Sleep

Cognitive-behavioural dysfunction
Affective disorders
Daytime fatigue
Autonomic changes

5. Children subject to sleep disturbances are more prone to attention deficit /hyperactivity behaviour[11]

6. The possibility exists that sleep disturbances can also lead to
Parasomnias
Weight excess
Immune system changes
Metabolic changes
Increased occurrence of accidents
Substance use/abuse *(evidence needed)*

Although more evidence should be gathered to substantiate these relations

7. For physiological reasons, children do not respond primarily to environmental stimuli with awakenings, but with arousals and sleep fragmentation. Therefore, children's sleep disturbance needs to be assessed using specific tools and methods.

8. Environmental stressors, such as noise, can alter the quantity and quality of sleep in children. Most findings have been related to short-term deprivations. The long-term effects of disturbed sleep due to chronic noise should be evaluated using longitudinal studies through adulthood.

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[11] References :
- Chervin RD, Archbold KH, Dillon JE, et al. "Inattention, hyperactivity, and symptoms of sleep-disordered breathing." *Pediatrics.* 2002;109:449–456
- Corkum P, Moldofsky H, Hogg-Johnson S, Humphries T, Tannock R. "Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication". *J Am Acad Child Adolesc Psychiatry.* 1999;38:1285–1293
- M. ThunstrÖm, "Severe sleep problems in infancy associated with subsequent development of attention-deficit/ hyperactivity disorder in 5.5 years of age", Acta Paediatrica 2002;91:584-592.
- Gregory A. et al, "Sleep problems in childhood: a longitudinal study of development change and association with behavioural problems". J Am Child Adolesc Psychiatry 2002; 41:964-971
- O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, Rutherford J, Mehl RC, Wang M, Tuell A, Hume BC and Gozal D. "Sleep and Neurobehavioral Characteristics of 5- to 7-Year-Old Children With Parentally Reported Symptoms of Attention-Deficit/Hyperactivity Disorder" *Pediatrics* 2003;111:554 –5

Recommendations

1. Sleep disturbances caused either by pathologies such as insomnia, sleep apnoea, narcolepsy, or by external factors such as work stress, light or tobacco smoke may be the origin of a number of disease states however, this has been insufficiently explored. Sleep disturbances caused by night noise (or day noise for shift workers) may be at the origin of this burden of disease, and its relative importance deserves to be evaluated more extensively.

2. It is difficult to identify a pathology creating sleep disturbance similar to that caused by noise. For the purpose of evaluating the global health impact of chronic long-term (over six months) sleep disturbance caused by noise exposure, the impact of chronic insomnia on health (described as a minimum of three awakenings per night with difficulties to fall back asleep for at least one month) will be used as a model.

3. To compare primary insomnia and sleep disturbance provoked by noise it is advisable to use standardized and well validated questionnaires designed to evaluate sleep disturbance in insomnia:

      i. Severity scale
     ii. Psychological scale
    iii. Pittsburgh sleep quality index[12]
    iv. Thoughts and beliefs sleep scale

4. The health consequences of usual coping strategies to deal with noise induced sleep disturbance should be evaluated. This covers the use of sedating and alerting drugs (e.g caffeine, tobacco, hypnotics, …)

5. There are important health effects of noise exposure that are observed during sleep and seem not to be associated with sleep disturbances. For public health purposes, these effects are important and need be explored in detail. They include cardiovascular diseases, and are mostly effects related to body responses to stress induced hormonal excretion.

6. Important aspects of the responses of sleep in children to environmental stressors and the resulting sleep deprivation need further evaluation. In particular, the potential effects of noise induced sleep deprivation on children' immune system, carbohydrate metabolism and endocrine functions should be evaluated.

7. Several longitudinal studies are needed in different countries following individual's polysomnographic and metabolic parameters and measures of noise, stress and health. In subgroups, intervention should include frequent blood sampling during sleep. Also, long-term experimental studies of disturbed sleep should be carried out with polysomnographic and metabolic measures.

8. A large epidemiological study should be undertaken on subjects exposed to night-time noise during which polysomnographic measures (PSG) and neuroimaging records (fMRI and PET) are performed. The study's aim would be to objectively measure changes in PSG in relation to noise exposure and to relate such changes to their localization in the brain (fRMI and PET).

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[12] Reference: Buysse DJ, Reynolds III CF, Monk TH, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

9. It is important to look at existing animal studies dealing with sleep deprivation, and more specifically with insomnia caused by noise

10. Sleep and noise researchers should use the commonly agreed upon terminology as described in the minutes of this meeting when using the terms: Normal sleep, Awakenings, Arousals, Sleep efficiency, Sleep deficit and Sleep fragmentation.

Policy

11. Since noise is an environmental factor that can be reduced through various technical means, it seems to be relevant and efficient to promote noise reduction campaigns for achieving improved sleep quality in the general population.

12. Traffic noise as well as neighbourhood noise play a significant role in terms of sleep disturbance. Besides noise reduction at the source, governments should provide various mechanisms, including financial support and programmes aimed at noise insulation of dwellings.
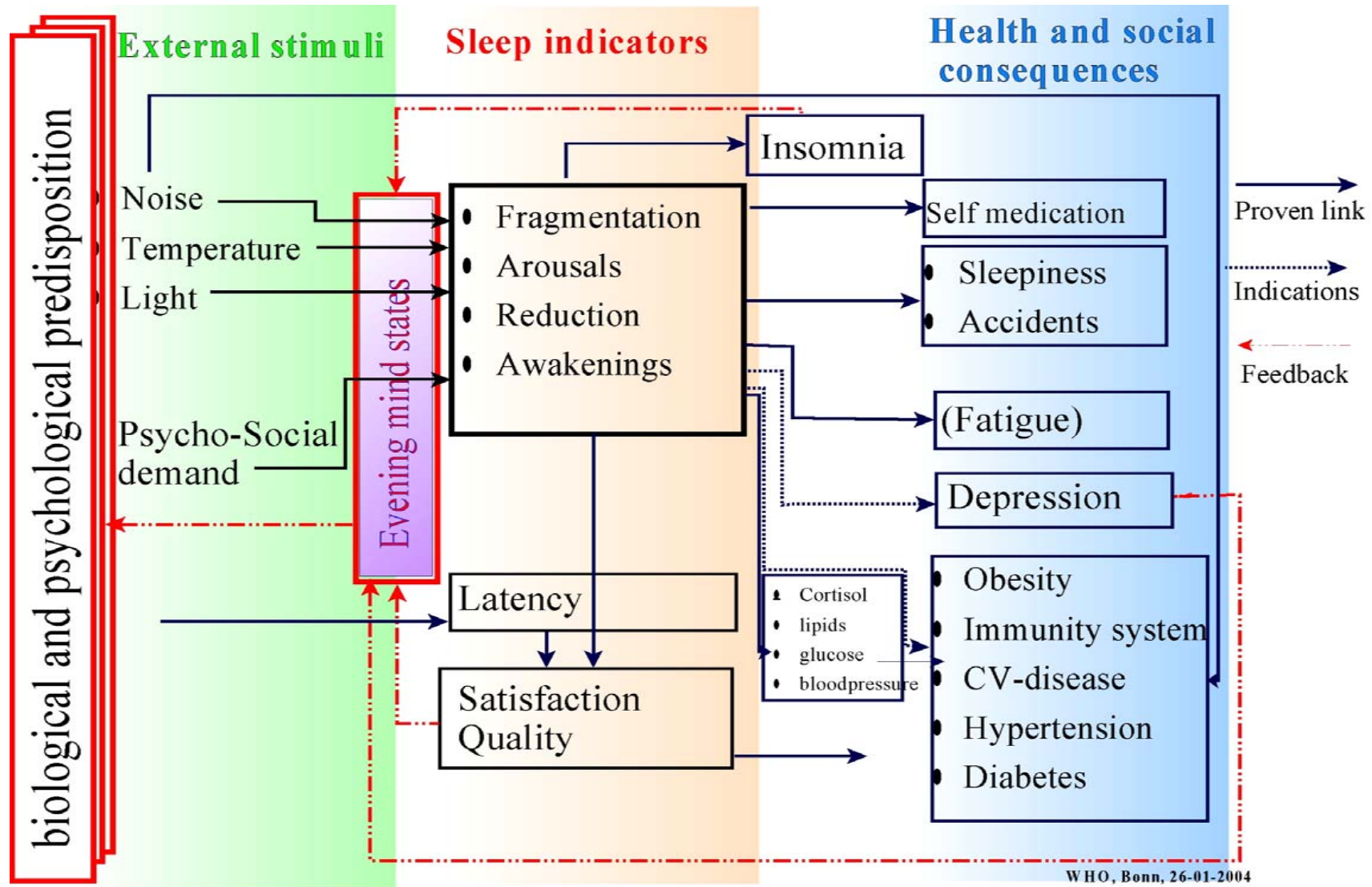
Figure 3 – Results of the working group 1

Annex 1 – Technical papers

1. Adult's sleep physiology; sleep quality and indicators of disturbed sleep. Main causes of sleep disturbances on adults - Alain Muzet

2. Sleep characteristics and sleep deprivation in infants, children and adolescents - André Kahn

3. Sleep disorders in adults; biological mechanisms through which sleep disorders affect the health of adults. Identification of environmental factors leading to clinical sleep disorders - Michel M. Billiard

4. Sleep disorders in children, mechanisms through which sleep disorders affect the health of children - Alfred Wiater

5. Medium and long term effects of sleep disturbance (by disorders and/or by stressors) on the health of adults - Sona Nevsimalova

6. Medium and long term effects of disturbed sleep on the health of children - Oliviero Bruni

7. Sleep - gender, age, stress, work hours - Torbjörn Åkerstedt

Adult's sleep physiology, sleep quality and indicators of disturbed sleep. Short-term effects on health of disturbed sleep in adults - Alain MUZET,

CNRS-CEPA, Strasbourg, France

1. Executive summary

The main purpose of this paper is to present a short overview of the physiological sleep process and describe its functions and structure. Objective sleep recordings and sleep questionnaires are used in a complementary approach to evaluate sleep normality and sleep quality. Examples of evolution of sleep stages are given to explain how the sleep process develops over time and progressively changes with age. Description of indicators of disturbed sleep involves disturbance factors, the responsiveness of the sleeper and how to measure it. Factors influencing the responsiveness of the sleeper are discussed and examples of short-term effects of disturbed sleep are presented.

2. Introduction

Sleep is a physiological state occurring in alternation with wakefulness, and its duration and quality are equally important for the quality of life. Indeed, waking and sleeping are not at all independent from each other and they cannot be separated. Our sleeping patterns have a direct influence on our waking behaviour and our daytime activities influence our sleep.

Sleep plays a fundamental role in the recovery process of fatigue but other functions can be dependent of it as well. It appears, however, to be quite fragile and responsive to external physical disturbing factors, but sleep complaints are certainly not always related to such events. In modern life, sleep appears to be a receptacle of aggression, tension, and anxiety and its disturbance can take several forms, from mild to severe.

Sleep phenomenon appears to be modifiable to a certain extend. It can be voluntarily reduced and its sudden reduction can be acceptable if not prolonged too much. Chronic sleep reduction on the other hand is the major problem to be addressed as cumulative effects are difficult to identify before they lead to clear pathologies. Therefore, the main questions are "how much" and "how long" can sleep be disturbed without any severe detrimental effects? In other words, does sleep disturbance, on the long run, lead to sleep pathologies or to global health effects? Unfortunately, these questions still remain unanswered until now.

Adult's sleep physiology, normal sleep and sleep quality

When discussing sleep physiology, we may be concerned with two fundamental research questions which are "why" and "how" do we sleep? Of course, these two questions are linked and a normal sleep development should be able to satisfy the exigencies of the functional role of sleep. Nevertheless, most of the time, the research effort has been focussed on "how we sleep?" and fewer works have been oriented to try to answer "why?". In fact, it seems easier to answer the first question than the latter. In fact, when sleep is normal, the question "why do we sleep" can be considered as futile. It

is when sleep is disturbed that this question is meaningful. The question is then: until which breaking point can sleep be disturbed and still meet its functional role? Or: are the functions of sleep endangered by sleep disturbance?

The sleep functions

The restorative function of sleep is obvious, but is it the only one? Is rest a substitute for sleep? Is there a whole series of functions and are there separated functions for the different sleep stages?

The early theories considered sleep as a mean of preventing fatigue and exhaustion (Claparède, 1908). The German physiologist Hess (1929, 1931), considered that sleep is a period where tropho tropic mechanisms of the nervous system provide the restitution of the energy lost during wakefulness through the ergo tropic mechanisms. This requires an equilibrium between somatic and autonomic functions. However, attempts to know what is "lost" during wakefulness and "recovered" during sleep have not been successful so far.

In more recent years, sleep functions have been considered as possibly separated between the two mains sleep states: orthodox and paradoxical (Rapid Eye Movement: REM) sleep. Orthodox, or synchronized sleep, could be assimilated to a state of sensory deprivation or cortical deafferentation, while REM sleep, or desynchronised sleep, would be a state where a homeostatic mechanism will bring back cortical excitation to some necessary level (Ephron & Carrington, 1966). This view of REM sleep as reactivated state, and the larger amount of REM sleep found in young animals, support the hypothesis of REM as a specific state of sensory stimulation.

Among the theories concerning the functions of REM sleep, Roffwarg et al. (1966) suggest that a certain amount of stimulation is necessary for a proper development of the young cortex. As the newborn or the young animal need more stimulation to the cortex than can be provided by sensory stimulation during the waking state, REM sleep would provide a kind of endogenous, sensory-like, stimulation of the brain. In the line of Moruzzi (1966), who suggest that sleep plays a role in the formation of engrams, or of Greenberg and Pearlman (1972), who hypothesized that REM sleep is involved in reprogramming the brain, Jouvet (1992) suggest that REM sleep is a perfect time for genetic printing in the brain. Several authors also consider REM sleep as playing a role in memory and learning processes (Breger, 1967; Hennevin & Leconte, 1971)

The sleep structure

When asking "how do we sleep?", we are describing mechanisms and how they are interrelated. For a very long time, the mysterious phenomenon of sleep was inaccessible to study. The technology which made this access possible relies on the electroencephalography method, developed by Hans Berger, in the 1920s. This technique provides a record of the natural electric activity of the brain and, by chance, the continuous recordings made during sleep appear to be quite characteristic and different from those obtained during waking (Loomis et al., 1935). In the 1950s, it was discovered that, at certain times during the night, the sleeper eyes were moving behind the closed lids, in a similar manner to eye movements occurring during wakefulness (Aserinky & Kleitman, 1955). When sleeper was awaken during these episodes, he or

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she was most often reporting to have dreamt, while this report was very infrequent when awakenings were performed at other times of the night.

The scientific exploration of the sleep process followed these first discoveries. The existence of two distinct types of sleep and the development of new recording techniques were sufficient reasons to begin this new era. Qualified at the beginning of "quiet" and "active" sleep, these two states were then named according to this specific eye motility, as Non Rapid Eye Movement sleep (NREM) and Rapid Eye Movement sleep (REM).

What is normal sleep? There is no definite rules for defining what normal sleep is. However, sleep normality can be estimated through the observation of sleep organisation or sleep structure. This means that sleep stages are present in their usual amount and their usual time occurrence during the night (see hypnograms in the following figures). However, the sleep structure depends on the age of the sleeper and some large variations can appear in the progressive modifications which develop with the aging process.

In order to be able to score the different sleep stages, it is necessary to associate EEG recordings with, at least, two other physiological variables: the eye movements and the electromyogram of facial or postural muscles. Most sleep laboratories associate other recordings to these three basic ones. This is the case for heart rate, respiratory rate, body temperature (core and skin sites), body movements, skin oxygen consumption, blood pressure, vasomotor phenomenon…. These supplementary recordings can bring additional information and are very useful in case of specific sleep disorders.

Sleep normally begins with NREM sleep, which is divided into four different sleep stages, from 1 to 4; stages 3 and 4 being often combined to form what is called slow wave sleep (SWS). The first step is the transition from wakefulness to stage 1. During this time, brain waves characteristic of relaxed wakefulness (alpha waves) gradually disappear and are replaced by the slower and larger theta waves. Then the transition from stage 1 to stage 2 is signed by the occurrence on the EEGs of characteristic burst of 13 to 15 Hz waves, lasting for one-half to two seconds, with a global shape of spindle. These "spindles" are accompanied by sharp spikes of high-voltage brain activity present on the different EEG leads and called "K complex". After some minutes, the electroencephalogram shows large undulations and those characteristic wave forms, occurring at about one-half to 2 cycles per second, are called "delta" waves. The amount of delta waves during the scoring period determines the current sleep stage. If less than 20 % of the period is occupied by delta waves, sleeper is considered as being still in stage 2. If the recording contains delta waves in 20 to 50 % of its length, this period is scored in stage 3, and it is scored stage 4 if this amount is larger than 50 % of the scoring period. In NREM sleep, sleeper lies quietly on the bed and brain waves are slow and regular.

NREM and REM alternate in cycles each of them lasting for approximately 90 minutes. In REM sleep, brain waves look quite closely to those recorded during wakefulness while extremities of the body are often subject to twitches and short movements contrasting with an almost paralysed body. In REM, regulatory mechanisms of the main physiological functions seem to be degraded. Thus, heart rate and respiratory rate are hectic and they fluctuate a lot. Thermoregulation is also degraded in REM sleep (Candas et al. 1979; Libert et al., 1982), which has been considered as a poïkilothermic state in

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animals (Parmeggiani & Rabini, 1970). The first REM period of the night, starting about 80 to 90 minutes after sleep onset, lasts for 3 to 5 minutes. The rapid eye movements occur by salves and not continuously during that period, while low muscle tone is permanent on the electromyogram recording.

This first set of NREM sleep stages followed by a REM sleep episode constitute what is called the first sleep cycle. It is followed by other cycles constituted almost the same way (see figure 1). Each NREM-REM cycle last for about 90 to 100 minutes. However, as sleep progresses, SWS becomes increasingly shorter and REM sleep episodes are progressively longer. Thus, in young adults, nearly all SWS occurs in the first half of the night, while only one third of total REM amount has been present during the same time.
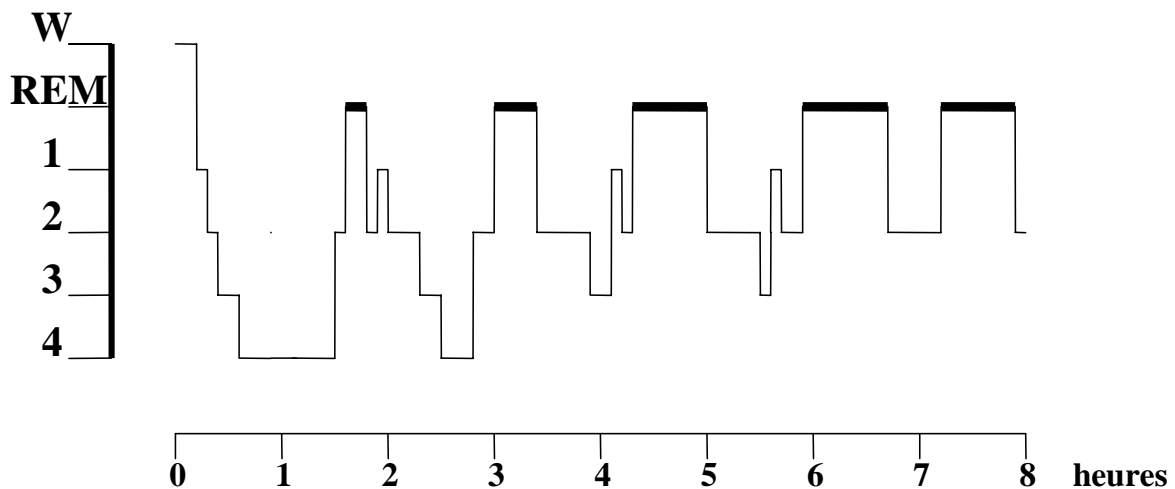
Figure 1: *Hypnogram of a young adult during a non disturbed sleep. Sleep onset occurs within 10 minutes after light out time (0). Sleep begins by NREM sleep stages and the first REM episode occurs some 90 minutes after sleep onset. SWS (stages 3 and 4) occurs mainly during the first 3 hours of the night. REM sleep episodes appear at very regular interval (90 to 100 minutes from the onset of one REM sleep episode to the next). This regular occurrence qualifies the REM cycle. No awakening is seen during the entire night.*

In SWS, heart rate and respiratory rate are stable and quite low, and the rate of metabolic activity throughout the brain is reduced by 30 %. During REM sleep, blood pressure, heart rate and respiratory rate fluctuate considerably. In people with chronically elevated blood pressure, REM related large fluctuations might be responsible for heart and arteries damages.

Body temperature falls during sleep and rises again shortly before usual awakening time. However, the nocturnal evolution of body temperature depends on the possible fluctuations of the ambient temperature (Dewasmes et al., 1994). The secretion of

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several hormones is tied to the sleep process. This is the case for example for growth hormone, prolactin, or rennin activity.

Body movements and body postural changes are parts of the sleep process. They certainly help to avoid prolonged constriction of parts of the body and redistribution of blood into the vascular bed (Muzet et al., 1972). During NREM sleep, body movements are reduced and even suppressed in SWS. In fact movements do not provoke systematically awakenings, nor sleep stage changes. The short arousal which is often associated with body movements last for a few seconds and the sleeper gets no conscious perception of it. Therefore, body movements are part of the natural sleep process and they cannot be considered as systematic responses to external stimuli.

Changes in the sleep structure with age

Adults average seven to nine hours of sleep per night, although a partial loss during the week is often recuperated on week ends. The changes in sleep that occur from young adult to old person are gradual and not always perceptible. However, the change in easiness to fall asleep and the increased frequency of nocturnal awakenings are clear indicators of the aging process affecting sleep structure.

In older subjects, the sleep structure can be quite different from those seen at younger age (see figure 2). The decline of SWS amount can start already at the age of 40 years. After the age of 60 years, NREM stages 1, and 2 and REM episodes constitute the majority of sleep content and waking episodes are frequent throughout the night, even if they are not lasting too long.
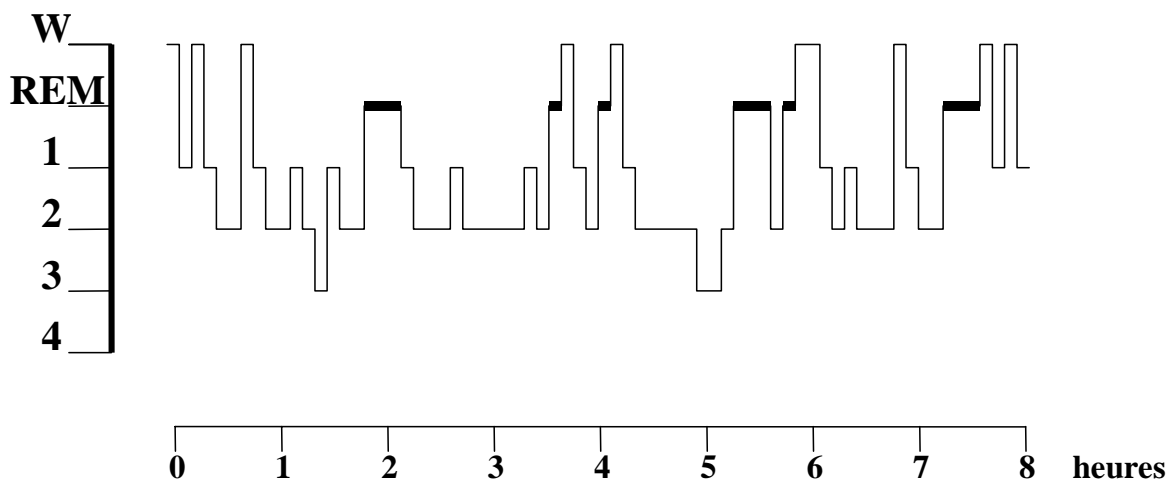
Figure 2: *Hypnogram of a 60 years old person. Sleep onset occurs in a normal delay, but it is followed by subsequent awakenings, giving the (false) impression of being delayed. The amount*

of SWS is tremendously reduced and stage 4 was never reached. REM sleep episodes occur almost as regularly as in younger age, but they often are fragmented. Sleep process is often interrupted by short lasting awakenings. Most of them occur during REM sleep episodes and terminate them.

Sleep quality

Sleep normality, as well as sleep quality, can also be estimated through the use of sleep questionnaires. There exist several sleep questionnaires and it is not exaggerated to say that most of the sleep laboratories have developed their own. Some contain a set of questions which are repeated over several days or weeks while others are proposing questions on a supposed "usual" night sleep. Most of the questions refer to sleep schedule, time taken to fall asleep, number and length of nocturnal awakenings, type of final awakening, type of sleep disturbance if any, global sleep quality and morning mood.

However, individual judgements about normality and quality, as any subjective assessment, can vary in large proportions between individuals, and sometime within individuals. In addition, there exist very few correlations between sleep quality estimates and the measured sleep stage structure (Moses et al., 1972; Muzet et al., 1973). These large discrepancies between the objective measure of sleep structure and the evaluation of sleep quality are even caricatured in some sleep pathologies such as the sleep apnoea syndrome (SAS) where patients often consider that their sleep is of rather good quality, even if it is restless.

As said before, sleep structure is changing with age and often so is sleep quality. Most people often consider their sleep quality to be worse with increasing age. This is mainly due to the fact that aged persons often wake up several times during the night, even for very short periods of time. They also consider their sleep to be more fragile and they often complain about external factors disturbing their sleep. It is obvious, however, that some unexpected associations between a spontaneous awakening and a non-related occurring noise are further described as noise-provoked awakenings. Therefore, and this is an important point to keep in mind, it is difficult to evaluate the normality and quality of sleep through the only subjective report of the sleeper.

3. Indicators of disturbed sleep

Sleep is a physiological state in which external stimuli are still perceived, although sleeper reactivity is seriously reduced. This reactivity may take different forms and, depending on the intensity of the stimulus, the observed responses can be strictly localised and limited to a part of the body or generalised to the entire organism, such as nocturnal awakening. In the first case, the responses of the sleeper are observed for rather small stimulus intensities and they are visible on a few physiological parameters (autonomic and/or motor responses, for example). In the second case, sleep disturbance is more global and effects can be seen on all physiological measures.

Disturbance factors

The immediate environment of the sleeper can be described in terms of physical parameters which contribute to the nocturnal comfort or uncomfort. Thus, the level of some of these parameters (ambient temperature, humidity, light, for instance) and the actual additional presence of other environmental parameters (such as noise and vibrations, for example) should be measured.

It is not always easy to identify the possible sources of sleep disturbance as, in the everyday life, there are often combinations of several environmental physical factors. It is, however, necessary to know their respective levels and also the amplitude of their possible variations as they determine the real exposure of the sleeper. It is surprising to note that despite of abundant scientific literature devoted to sleep, there are only a few works taking into account the impact of environmental factors on human sleep. Among those, there exist a disproportion between the rather large number of papers dealing with the effects of noise on sleep and the very few devoted to the effects of other factors such as ambient temperature and humidity, ambient lighting, barometric pressure, magnetic field or air quality.

Responsiveness of the sleeper

Of course, the reactivity of the sleeper depends on the ability to detect stimuli through the specialised sensorial organs and the transmission of their signals to the corresponding central nervous system areas. However, detection thresholds can be largely modified during sleep. Therefore, the elevation of the detection threshold, which implies a larger stimulus intensity to reach the reaction threshold, is only visible through the physiological responses measured by specific instruments and not through the verbal report of the sleeper.

As said before, depending on the nature and physical characteristics of the stimulus, it is possible to see all possible reactions, from discrete and very localised responses affecting a single physiological variable to major and unspecific sleep disturbance. Thus, a physical factor able to modify very quickly its characteristics, such as noise, can provoke very rapid responses occurring within a few seconds only after the start of the stimulation (Muzet & Naitoh, 1977; Muzet, 1989). A physical factor varying slowly, such as ambient temperature, provokes modifications which are much more difficult to detect as they occur more progressively, although their amplitude and their final impact on the sleep structure can be important.

The measure of responsiveness during sleep

The simple visual observation of the sleeper allows to detect some of the immediate effects due to disturbing events, such as lengthening of falling asleep delay, sudden awakening, body movement or postural change. However, polygraph recording of EEGs, body movements, heart rate and respiratory rate, vasomotor responses and blood pressure of the sleeper, give more details about the evolution of sleep process, but they remain most often reserved to the sleep laboratory. These recordings make possible the detection of immediate effects due to the disturbing factor.

These immediate effects can be:

- Electroencephalogram modifications, which sign moderate or profound changes of the sleep structure, from discrete arousal to sleep stage change or awakening;
- Modifications of heart and respiratory rates and amplitudes, often associated to concomitant cardiovascular changes (vasomotor and blood pressure changes);
- Motor responses, from light movement of a limb to global postural change.

These responses can be observed isolated or associated, depending on the importance of the sleep disturbance. They are most of time occurring without any consciousness from the sleeper, except for prolonged awakenings.

Sleep stage distribution can be modified over the disturbed night. Fragmented or interrupted slow wave sleep episode at the beginning of the night might be compensated by another SWS episode occurring later during the same night. Similarly, Naitoh et al. (1975) have shown that rhythm of REM sleep was notably modified by the effects of external factors (noise and ambient temperature) on sleep. Figure 3 gives an example of hypnogram of a noise-disturbed night.
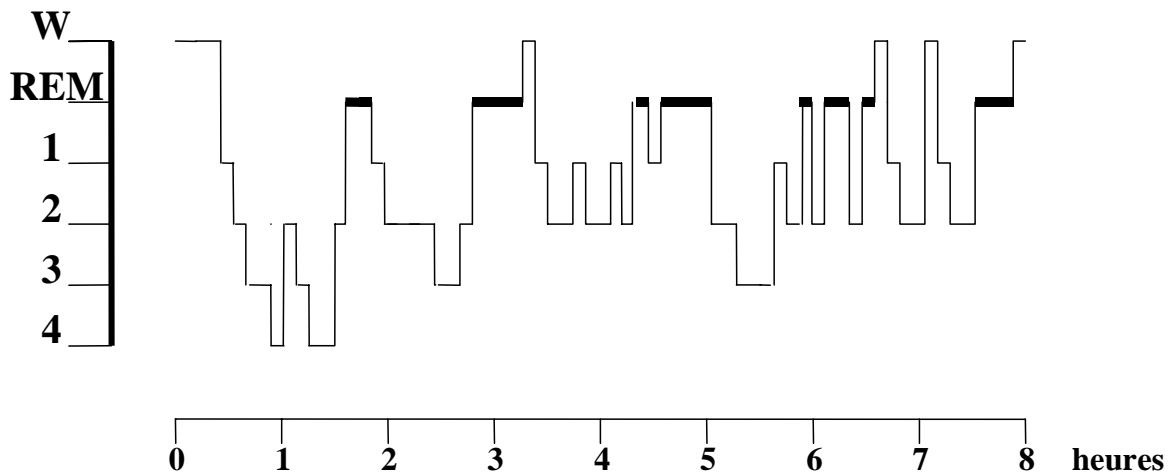
Figure 3: Hypnogram of a young adult in a noise-disturbed night. Sleep onset is slightly delayed. The first episode of stage 4 is partly interrupted. A significant amount of SWS does occur during the 5th hour (as a compensatory mechanism of the disturbed first episode?). REM sleep still shows clear rhythmic occurrence but some of the episodes are fragmented. Significant awakenings occur throughout the sleep process. Sleep efficiency is reduced.

Subjective complaint of disturbed sleep

The subjective complaint of bad sleep can be reported in the following morning either spontaneously or in response to specific questions. However, as stated earlier, subjective estimates and objective measures of disturbed sleep are often not

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superimposed. Thus, some sleepers complain about poor sleep quality while no major sleep structure modifications can be observed through the physiological recording. In the reverse, it has been shown that under moderate noise exposure, most sleepers show progressive subjective habituation to their noisy environment, while their physiological responses to noise remain permanent over long exposure periods (Muzet & Ehrhart, 1980; Vallet et al., 1983).

Factors influencing sleeper responsiveness

The study of sleeper responsiveness is particularly complex due to the multiplicity of factors to be taken into account. To the characteristics of the stimulus, must be added the type of sleep, individual factors, and possible situational factors.

Stages of sleep and deepness of sleep

The classical evaluation of responsiveness is generally performed by the determination of the awakening threshold. The first evaluation of sleep deepness has been based on the awakening threshold due to noise stimulus, using different intensities and applied at different times of the night (Kohlschütter, 1862). This author found a tremendous increase of the awakening threshold at the end of the first hour of sleep, and then an important decrease of this threshold at the end of the third hour of the night. Michelson, in 1897, found a curve showing comparable variations of the awakening threshold but with several undulations. Whatever the stimulus used, all evaluations showed the existence of a deep sleep period during the two hours following falling asleep, and then a shallower stage of sleep during the following hours.

The first studies using electroencephalogram have shown that it was possible to use the abundance on some specific EEG activities, and consequently the sleep stages, as indicators of change in the responsiveness of the sleeper exposed to external stimuli (Blake & Gerard, 1937; Blake et al., 1939). From these studies, it has been suggested that EEG could be used as an indicator of deepness of sleep.

However, it appears quite clearly that there is a large variability is the capacity to observe an awakening for a given stage of sleep and for a well calibrated stimulus. The fluctuation of the awakening threshold can be considerably large for a given individual and from one night to the next (Kleitman, 1963). When Rapid Eye Movement sleep stage (REM sleep) was first described, it appeared clearly that the awakening threshold seen in this particular state was much higher than that observed in stage 1, although their EEG characteristics are quite similar. A classic study performed by Rechtschaffen et al. (1966), has shown that, although the awakening threshold is generally the highest in stage 4, the threshold obtained in REM sleep is most often higher than that seen in stage 2, and that awakening is obtained in these two stages with a lower intensity in the second half of the night than during the first half. This result suggest that, for a given sleep stage, the awakening thresholds decrease progressively throughout the night (Keefe et al., 1971).

In fact, numerous studies have shown that awakening threshold in REM sleep is extremely variable. More than for any other sleep stage, stimulus signification plays an

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important role in the probability to observe an awakening in this state. This remark applies also, but with a lesser degree, to other sleep stages. Already in 1937, Loomis et al. have found that a sleeper response to noise stimulus was not mainly related to the noise intensity but rather to its intrinsic signification. This aspect was also considered by Oswald et al. (1960) who suggested that the subjective signification of a stimulus was more important than its physical characteristics.

Individual factors

Among the most frequent considered individual factors, we can cite age, sex and psychological profile. When using sound stimuli there exist a difference in EEG responses between children and adults, the former group exhibiting a lower brain wave reactivity to the stimulus than the latter one. However, this result contrasts with a cardiovascular reactivity which is quite identical throughout the different age groups (Muzet et al., 1981).

It is difficult to find any difference between men and women in localised physiological responses, although young males seem to have a more disturbed sleep than young female subjects, while this difference tends to reverse at age older than 30 years (Lukas, 1972; Muzet et al., 1973).

The individual attitude towards an expected awakening due to an identified stimulus, are in part explaining the large differences observed between individuals. However, taking as a criteria the self-estimation of sensitivity to noise (purely subjective evaluation), there was no significant difference in measured cardiovascular reactivity during sleep between subjects estimating themselves as highly sensitive to noise and subjects considering to be no sensitive to it, although clear difference in reactivity appeared between the two groups during their waking state (Di Nisi et al., 1990).

Situation factors

Situation factors are numerous and some of them might have a modulator effect on sleep reactivity. Some of these factors can be consciously manipulated. This is the case for prior sleep deprivation. In this case, after a total sleep deprivation, recovery sleep is characterised by a marked increase in awakening thresholds (Naitoh 1976; Williams et al., 1964).

Pharmacological manipulation of sleep can modify the sleeper responsiveness to noise. But after a sleeping medication intake, there exist a dissociation between a global disturbance (awakenings) which is reduced, and the more localised responses (cardiovascular responses, for instance) which are not modified (Muzet et al., 1983). It is also necessary to underline that the elevation of the awakening thresholds observed with some sleeping medications (Johnson et al., 1979; Spinweber et al., 1982) can lead to major consequences when sound is used to warn the sleeper about an imminent danger (Johnson et al., 1987).

4. Short-term effects of disturbed sleep

We here define short-term effects as effects occurring within a few hours or a few days after sleep has been disturbed. There is, of course, a large variability in the latency of the secondary effects due to the variation of responsiveness from one individual to another. Thus, some individuals might hardly be affected by repeated but moderated sleep deprivation, while others can react after a single sleep deprivation of a few hours.

Subjective complaints about poor sleep quality, associated or not with fatigue and change in mood, are often the most prominent manifestations of sleep disturbance. Thus, sleep quality was used by Lukas as a measure of sleep disturbance effect (Lukas, 1975). Decreased mood and increased tiredness have been related to a decrease in perceived sleep quality which, in turn, leads to decrease performance (Öhrström, 1989).

In some cases, increased drowsiness during daytime and the need for compensatory sleep period (such as a day nap), are the signs of unsatisfactory sleep quality and amount. These short-term effects can exist more or less permanently, depending on the duration of the sleep disturbance. They may have severe consequences in term of work ability and work accidents. For instance, following noise-disturbed nights, basic psycho-sensory-motor tasks such as simple or complex reaction time tests show a lengthening of the responses (Wilkinson & Campbell, 1984; Öhrström & Rylander, 1990). These effects are certainly not absolutely noise-specific and they are obviously related to the sleep disturbance *per se*.

The major disturbance of sleep is obviously the reduction of its duration. Although we know that it is possible to reduce the amount of sleep voluntarily on a short term basis without any severe consequence, it is not the case when sleep reduction is chronic over a long period of time. Prolonged sleep deprivation leads to chronic fatigue, excessive sleepiness, decrease in motivation and reduction in daytime performance. Specific workers who are engaged in high responsibility jobs, often show high anxiety level because they have to perform difficult tasks and they need high resources and restful sleep.

One of the most important effect of sleep disturbance remain the use of medication, under or without the supervision of a medical specialist, and this seems to be particularly accentuated in old age persons. The medical consumption has been increasing during the last decades, and sleep disturbance, and subsequent poor daytime life quality, are certainly among the major complaints which drive patients to their medical doctor. Thus, the excess of drug consumption appears to be one of the main challenges of tomorrow.

5. Conclusions

Sleep, as a physiological state, is necessary for the well being of the living organism. Its interactions with daytime activities are profound and they determine the global equilibrium between these two fundamental states: sleep and wakefulness. Sleep normality and sleep quality concepts are used in the everyday life, although it is often difficult to state clearly how to define them. Sleep structure is changing over time and this progressive evolution is quite variable from one individual to another. The sleep quality concept may also considerably vary from one person to another as subjective expectancy is highly variable and complex. Therefore, sleep disturbance has often to be considered on an individual basis as far as sleep quality is concerned. There exist obvious indicators of disturbed sleep structure as well as changes in main physiological

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functions during sleep. However, the significance of these modifications in term of global health is often disputable. We certainly need to focus more our interest into the possible cumulative effects of long-term sleep disturbance, in order to be able to prevent populations against more or less well identified disturbance sources.

6. References

Aserinsky E, Kleitman N. Two types of ocular motility occurring in sleep. *Journal of Applied Physiology* 1955; **8**: 1-10.

Blake H, Gerard RW. Brain potentials during sleep. *American Journal of Physiology*, 1937, **119**: 692-703.

Blake H, Gerard RW, Kleitman N. Factors influencing brain potentials during sleep. *Journal of Neurophysiology*, 2, 48-60, 1939.

Breger L. Functions of dreams. *Journal of Abnormal Psychology*. Monograph n° 641, 1967.

Candas V, Libert JP, Vogt JJ, Ehrhart J, Muzet A. Body temperature during sleep under different thermal conditions. In: *Indoor Climate: Effect on Human Comfort, Performance and Health*, PO Fanger and O Valbjorn (eds), Danish Building Research Institute, Copenhagen, 1979, pp. 763-775.

Claparède E. La fonction du sommeil. *Revista di Scienza*, 1908, **2** : 141-158.

Dewasmes G, Nicolas A, Rodriguez D, Salamé P, Eschenlauer R, Joly D, Muzet A. Human core temperature minimum can be modified by ambient thermal transients. *Neurosciences Letters*, 1994; **173**: 151-154.

Di Nisi J, Muzet A, Ehrhart J, Libert JP. Comparison of cardiovascular responses to noise during waking and sleeping in humans. *Sleep*, 1990, **13**: 108-120.

Ephron HS, Carrington P. Rapid eye movement sleep and cortical homeostasis. *Psychological Reviews*, 1966, **73**: 500-526.

Greenberg R, Pearlman C. REM sleep and the analytic process: a psycho-physiologic bridge. *Report to the American Psychoanalytical Association*, New York, 1972.

Hennevin E, Leconte P. La fonction du sommeil paradoxal : faits et hypothèses. *L'Année Psychologique* n°2, 1971.

Hess WR. The mechanism of sleep. *American Journal of Physiology*, 1929, **90**: 386-387.

Hess WR. Le sommeil. *Comptes-rendus de la Société de Biologie*, 1931, **107** : 1333-1364.

Johnson LC, Church MW, Seales DM, Rossiter WS. Auditory arousal thresholds of good and poor sleepers with and without flurazepam. *Sleep*, 1979, **1**: 259-270.

Johnson LC, Spinweber CL, Webb SC, Muzet A. Dose level effects of triazolam on sleep and response to a smoke detector alarm. *Psychopharmacology*, 1987, **91**: 397-402.

Jouvet M. *Le sommeil et le rêve*. Editions Odile Jacob, Paris, 1992.

Keefe FB, Johnson LC, Hunter EJ. EEG and autonomic response pattern during waking and sleep stages. *Psychophysiology*, 1971, **8**: 198-212.

Kleitman N. *Sleep and wakefulness* (2nd ed.), The University of Chicago Press, Chicago, 552 pp, 1963.

Kohlschütter E. Messungen der Festigkeit des Schlafes. *Zeitschrift rational Medizin*, 1862, **17**: 209-253.

Libert JP, Candas V, Muzet A, Ehrhart J, Vogt JJ. Thermoregulatory adjustments to thermal transients during slow wave sleep and REM sleep in man. *Journal of Physiology (Paris)*, 1982; **78**:251-257.

Loomis A, Harvey EN, Hobart G. Potential rhythms of the cerebral cortex during sleep. *Science*, 1935 ; **81** (2111) : 597-598

Loomis AL, Harvey EN, Hobart G. Cerebral states during sleep as studied by human brain potentials. *Journal of Experimental Psychology*, 1937, **21**: 127-144.

Lukas JS. Awakening effects of simulated sonic booms and aircraft noises on men and women. *Journal of Sound and Vibrations*, 1972, **20**: 457-466.

Lukas JS. Noise and sleep: A literature review and a proposed criterion for assessing effect. *Journal of the Acoustical Society of America,* 1975; **58**: 1232-1242.

Michelson E. Untersuchungen ueber die Tiefe des Schlafes. *Psychologisch Arbeiten*, 1897, **2**: 84-117.

Moruzzi G. The functional significance of sleep with particular regard to the brain mechanisms underlying consciousness. In: Brain Mechanisms and Conscious Experience, Eccles JC (ed), New York, Springer Verlag, 1966, pp. 345-388.

Moses J, Lubin A, Naitoh P, Johnson LC. Reliability of sleep measures. *Psychophysiology*, 1972; **9**: 78-82.

Muzet A, Becht J, Jacquot P, Koenig P. A technique for recording human body posture during sleep. *Psychophysiology*, 1972; **9**: 660-662.

Muzet A, Schieber JP, Olivier-Martin N, Ehrhart J, Metz B. Relationship between subjective and physiological assessments of noise-disturbed sleep. U.S. Environmental Protection Agency, Report n°550/9-73-008, pp. 575-586, 1973.

Muzet A, Naitoh P. Sommeil et bruit. *Confrontations Psychiatriques*, 1977, **15**: 215-235.

Muzet A, Ehrhart J. Habituation of heart rate and finger pulse responses to noise during sleep. In Tobias JV et al. (eds), *Noise as a Public Health Problem*, Rockville, Maryland, ASHA report n°10, 1980, pp. 401-404.

Muzet A, Ehrhart J, Eschenlauer R, Lienhard JP. Habituation and age differences of cardiovascular responses to noise during sleep. In : *Sleep 1980*, Karger, Basel, pp. 212-215, 1981.

Muzet A, Weber LD, Amoros C, Ehrhart J, Libert JP, Tsakona C. Electrophysiological and cardiovascular responses to noise during sleep. Effects of a benzodiazepine hypnotic. In : *Noise as a Public Health Problem*, G. Rossi (ed), Centro Ricerche E Studi Amplifon, Milano, pp. 985-993, 1983.

Muzet A. Les effets du bruit sur le sommeil. *Comptes-rendus de la Société de Biologie*, 1989, **183**: 437-442,

Naitoh P. Sleep deprivation in human subjects : a reappraisal. *Waking and Sleeping*, 1976, **1**: 53-60.

Naitoh P, Muzet A, Lienhard JP. Effects of noise and elevated temperature on sleep cycle. 2nd International Congress of Sleep Research. In: *Sleep Research 4,* Edimburgh, 1975, pp. 174.

Öhrström E. Sleep disturbance, psycho-social and medical symptoms. A pilot survey among persons exposed to high levels of road traffic noise. *Journal of Sound and Vibration*, 1989; **133**: 117-128.

Öhrström E, Rylander R. Sleep disturbance by road traffic. A laboratory study on number of noise events. *Journal of Sound and Vibration*, 1990; **143**: 93-101.

Oswald I, Taylor AM, Treisman M. Discriminative responses to stimulation during human sleep. *Brain*, 1960, **83**: 440-453.

Parmeggiani PL, Rabini C. Sleep and environmental temperature. *Archives Italian of Biology*, 1970; **108**: 369-387.

Rechtschaffen A, Hauri P, Zeitlin M. Auditory awakening thresholds in REM and NREM sleep stages. *Perceptuals and Motor Skills*, 1966, **22**: 927-942.

Roffwarg H, Muzio J, Dement W. Ontogenic development of human sleep-dream cycle. *Science*, 1966, **152**: 604-618.

Spinweber CL, Johnson LC. Effects of triazolam (0.5 mg) on sleep, performance, memory and arousal threshold. *Psychopharmacology*, 1982, **76**: 5-12.

Vallet M, Gagneux JM, Clairet JM, Laurens JF, Letisserand D. Heart rate reactivity to aircraft noise after a long term exposure. In: "*Noise as a public health problem*", ROSSI G. (ed), Centro Ricerche E Studi Amplifon, Milano, 1983, 965-971.

Wilkinson RT, Campbell KB (1984). Effects of traffic noise on quality of sleep: assessment by EEG, subjective report, or performance the next day. *Journal of the Acoustical Society of America*, 1984; **75**: 468-475.

Williams HL, Hammack JR, Daly RL, Dement WC, Lubin A. Responses to auditory stimulation, sleep loss and the EEG stages of sleep. *Electroencephalography and clinical Neurophysiology*, 1964, **16**: 269-279.

Sleep characteristics and sleep deprivation in infants, children and adolescents - Kahn A, Franco

P, Groswasser J, Scaillet S, Kelmanson I, Kato I, Sawagushi T,

Marzuriewci H, Dan B

University Pediatric Hospital Queen Fabiola, Brussels, Belgium

Corresponding author:

Pr A. Kahn

Hôpital Universitaire des Enfants Reine Fabiola

Av J.J. Crocq, 15

B-1020 Bruxelles

Belgium

E-mai : akahn@ulb.ac.be

Tf: + 32.2.477.32.37

Fax: + 32.2.477.27.55

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Summary

In this review, we discuss usual sleep recording techniques, normal sleep characteristics and the effects of sleep deprivation. Sleep quality and quantity mature while the child ages. Sleep-wake behaviors are described in fetuses, infants, children and adolescents. The short-tem and of medium-term effects of sleep deprivation are reviewed. While abundant literature exists on the physiology and characteristics of children's sleep, only sparse empirical data are available on the effects of sleep losses on children's physical, cognitive, mood, and mental health functions.

I. Introduction

There is a large body of knowledge about the effects of age and brain maturation on sleep behavior. Sleep characteristics may be modified by environmental sources of annoyance, such as noise. When sufficiently severe, these stressors interfere with sleep and appear to affect mood, behavior, cognitive, cardiovascular and autonomic regulation. These aspects of sleep are reviewed in this document, that relies on published reports with a literature search conducted with the use of PubMed and MedLine (with as key words: sleep, sleep deprivation, infant or children), as well as personal clinical experience in children's sleep (Kahn et al. 1996; Kahn et al. 2002).

II. Background

The study of sleep characteristics in children depends largely on recording and scoring techniques. Excellent reviews are available for further readings (Coons and Guilleminault, 1982; Brouillette, 1992; Curzi-Dascalova and Mirmiran, 1996).

II.1. Sleep recording

II.1.1. Techniques
There has been a lack of agreement regarding the techniques best used for data acquisition in children. For newborns, some investigators have suggested direct observation of the infant (Prechtl, 1964). In young infants, scoring systems based on the recording of body movements have been developed (Sadeh et al. 2000). Some researchers have recommended limiting the recording to cardiac or respiratory variables (Haddad et al. 1987). A number of reports have been based on pneumograms or respirograms, which combine cardiac and respiratory derivations (Flores Guevara, 1987). Other authors have recommended the use of complete polysomnographic studies (Brouillette, 1992).

II.1.2. Timing and duration
Sleep studies in children also differ concerning the timing and duration of the recordings. Some studies have been done during daytime naps (Emde and Walker, 1976), others during the night (Brouillette, 1992). There are important differences between short daytime nap studies and whole night recordings, because of the influence of circadian rhythms. During nighttime recordings of infants, twice as many apnea occur in Rapid Eye Movements (REM) sleep and six times as many in Non-Rapid Eye Movements (NREM) sleep, than during short nap studies (Hoppenbrouwers et al, 1979). In addition, REM sleep dominates the morning naps and NREM sleep the afternoon naps. Time until sleep onset and REM latencies are also significantly shorter in afternoon naps than during other sleep onsets (Emde and Walker, 1976).

Sleep studies in children may also differ because of environmental conditions. Significant differences are seen between studies performed in sleep laboratories, hospital wards, neonatal units and at home (Bernstein et al. 1973; Katona et al. 1980).

II.2. Sleep scoring

For the scoring of sleep recordings, joined epochs of set duration are considered for scoring. Various lengths of scoring periods may be chosen, but usually 30-second periods of the recordings are analysed. The entity termed "state" is then derived from a cluster of attributes of different physiologic variables (Harper et al. 1981). According to criteria recommended in the literature (Anders et al. 1971; Guilleminault and Souquet, 1979). States are categorized as: NREM sleep, also termed Quiet sleep; REM, or Active sleep; "Indeterminate sleep", and Wakefulness. In the first months of life, NREM is usually classified as Quiet sleep, and REM as Active sleep. On polygraphic recordings, Indeterminate sleep corresponds to a state in which criteria for neither REM nor NREM can be met (Anders et al. 1971). During Active sleep, bursts of binocularly synchronous rapid eye movements under closed eyelids are seen. These rapid eye movements are numerous in newborn infants, decrease during the first weeks of life, and occur in bursts separated by periods without ocular motility after 3 or 4 months of life. During Active sleep, sucking movements, fine twitches, tremors, grimaces, and smiles occur together

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with intermittent stretching and large athetoid limb movements. Heart rate and respiration are irregular, concomitantly with phasic eye movements. No or highly instable activity is recorded from the chin electromyogram. Quiet sleep seems more basal and regulated. It is characterized by minimal movement, except for irregularly occurring, sudden, generalized movements called startles, which become rare after the newborn period. There are no movements of the eyeballs, but after the newborn period, slow, regular rolling movements may occur. Cardiac and respiratory rhythms are regular (Parmelee et al. 1972).

Analysis conventions of sleep recordings vary widely among investigators, leading to discrepancies in data interpretation (Reite et al. 1995). Manuals have been developed that include both behavioral and polygraphic features (Anders et al. 1971). Some have been adapted to fit electroencephalographic (EEG) changes in infants older than 3 months (Guilleminault and Souquet, 1979). For infants aged less than 3 months, it may be difficult to score sleep stages adequately. In the newborn period, EEG characteristics of REM and NREM sleep vary by subtle differences in voltage and frequency. At this age, non-EEG parameters, such as chin muscle (EMG) tone, phasic twitches, rapid eye movements, and respiratory regularity are the most useful features in distinguishing sleep stages and wakefulness (Anders et al. 1971).

In order to study 'arousals', specific definitions are used in infants, as the scoring methods used in adult sleep studies can be applied to older children, but not to infants under 1 year of age. The International Pediatric Wake-Up Club has elaborated in 2001, a method for the scoring of arousal in infants aged between 1 and 6 months. Arousals are separated into subcortical activity and cortical arousals. A subcortical activity is defined by the presence of body movements and/or autonomic changes in breathing and heart rates, not accompanied by changes in EEG frequency or amplitude. A cortical arousal corresponds to the simultaneous presence of autonomic and EEG changes. An awakening is scored when the infant cried and/or opened the eyes. An arousal or an awakening threshold reflects the tonic state of an unknown adaptive mechanism, or mechanisms, which permit sleep to continue in the face of stimuli, which normally elicit responses during wakefulness, but also permit awakening to some stimuli. The clinical importance of malfunction of these mechanisms, as in the easily disturbed sleep of insomniacs, is apparent (Rechtschaffen et al. 1966). The opposite inability to arouse has been demonstrated in infants who died of Sudden Infant Death syndrome (Kato et al. 2003).

Scoring is usually done visually by at least two independent scorers to ensure reliability. Computerized scoring systems have been developed. Scoring may differ significantly between visual and software-based analysis (Reite et al. 1995).

III. Normal sleep characteristics in children   (Table I)

Some major sleep-wake behaviors and related characteristics seen during sleep studies are summarized in the following paragraphs.

III.I.   Sleep-wake behavior

III.I.1. In utero
The mechanisms that control sleep-wake rhythms develop well before birth. In the human fetus, spontaneous movements can be identified by ultrasound visualization at

about 10 weeks of gestation. It is not known whether the fetus is truly awake (Prechtl, 1974), although certain movement patterns are reminiscent of postnatal movement patterns during wakefulness (Hoppenbrouwers et al. 1978). Rhythmical cycling of activity is recorded in utero between 20 and 28 weeks (Parmelee et al. 1967; Sterman and Hoppenbrouwers, 1971). The fetal rest-activity pattern is characterized by long silent periods that last minutes to hours, during which time there are no respiratory movements (Dawes et al. 1972). Cycling times tend to vary between 40 and 60 min (Sterman and Hoppenbrouwers, 1971). The periods of quiescence or sleep represent 53% of the time at 30 weeks' conceptional age and increase to 60% near term. The human fetus spends most of its time in a state equivalent to sleep, similar to that recorded in newborn infants (Njhuis et al. 1982). The healthy fetus in utero reacts to external noises. This is the result of the development of the human cochlea and peripheral sensory end organs. These complete their normal development by 24 weeks of gestation. Sound is well transmitted into the uterine environment. Ultrasonographic observations of blink-startle responses to vibroacoustic stimulation are first elicited at 24 to 25 weeks of gestation, and are consistently present after 28 weeks, indicating maturation of the auditory pathways of the central nervous system (Committee, 1997).

III.I.2.   Preterm infants
In the premature infant of 31 weeks' conceptional age, respiratory regularity is informative about sleep state (Curzi-Dascalova et al. 1983). Breathing patterns, such as respiratory pauses or phasic relationships between thoracic and abdominal respiration, help to distinguish between Quiet sleep and Active sleep. In premature infants, Quiet sleep can be identified by the 32nd week of gestation (Parmelee et al. 1972). In infants born before 36 weeks'gestational age, percentages of Active sleep are elevated and those of Quiet sleep reduced compared with later ages. There is also more Indeterminate sleep (Parmelee et al. 1967). In infants born after 36 weeks' gestational age, sustained sleep states can be identified, with cycle times varying between 40 and 60 min (Sterman et al. 1971).

When premature infants reaching 40 weeks' gestational age are compared with term infants at comparable gestational ages, most cardiorespiratory differences vanish, but they still have a higher respiratory frequency than newborn at term (Curzi-Dascalova et al. 1983). Premature infants spend more time awake at the expense of active sleep (Parmelee et al. 1967), and their sleep states tend to remain more poorly organized, showing a lack of concordance between behavioral and EEG variables. This pattern continues until 6 months of age (Gaultier, 1987). Ultradian sleep cycle is shorter in full-term infants compared with conceptional age-matched preterm infants.

III.I.3. From birth to 12 months of life

Total sleep time per 24 h lasts about 16 to 17 h in the newborn period, decreases to 14 to 15 h by 16 weeks of age, and decreases to 13 to 14 h by 6 months of age (Parmelee et al. 1967). In newborns, sleep and wakefulness follow an ultradian rhythm of about 4h. The development of a well-defined circadian sleep-wake pattern is preceded by a free-running cycle of about 25 h, similar to the free-running cycle seen in adulthood (Hoppenbrouwers et al. 1982). An ultradian sleep cycle is identified between 4 and 6 weeks of age, when sleep begins to consolidate in relation to the light-dark cycle. A priming of circadian sleep-wake cycle seems to be organized by the feeding cycle.

It takes several months before a regular circadian sleep-wake cycle is installed and before the infant sleeps through the night. By 1 month of age, infants' sleeping periods are longer during the night, and a sustained awakening begins to occur in the early hours. Long sleep periods shift to nighttime by 2 to 3 months of age, when the conjunction of environmental and developmental factors leads to the organization of a predictable and stable diurnal distribution of wakefulness and sleep (Parmelee et al. 1972). The longest sleep periods gradually lengthen to 8 or 9 h of sleep time by 1 year of age (Anders and Keener, 1985).

There is a need to distinguish between nighttime quiet awakenings and nighttime crying, which often leads to removal from the crib. Some infants cry to signal their parents and are labelled night wakers, whereas others are able to soothe themselves and return to sleep (Anders and Keener, 1985). Sleeping through the night is reported for 44% of 2-month-old infants (Hoppenbrouwers et al. 1982; Anders and Keener, 1985). Waking may increase again during the second 6 months of life (Anders and Keener, 1985). By 1 year of life, premature infants are better able to return to sleep on their own than full-term infants, who are more likely to be taken from their crib (Anders and Keener, 1985). During the day, wakefulness steadily increases as daytime sleep becomes consolidated into well-defined daytime naps (Parmelee et al. 1972). Daytime sleep occurs in three or four naps at 6 months and in two naps by 9 to 12 months of age.

III.I.4. Preschool children (1 to 5 years)
During early childhood and preschool years, changes in sleep-wake characteristics occur more slowly than during the preceding months of life. The total amount of sleep decreases slowly from 15 h at 1 year of life, to 13 to 14 h by 2 years, and 12 h by 4 years. The progressive reduction in total sleep time is due mainly to a decrease in daytime sleep. Nighttime sleep becomes consolidated into long periods of approximately 10 h (Kohler et al. 1968). During the first 3 years of life, short naps occur in the midmorning and early afternoon. The modal duration of naps is about 2 h. The morning naps disappear, and by 3 to 5 years of life, the afternoon naps gradually disappear.

Older preschoolers are more likely to exhibit a prolongation of bedtime routine, insist on sleeping with the light on, take a treasured object to bed, request parental attention after being told "good night", and experience more delays in falling asleep than when younger. The frequency of night awakening remains low in the normal preschool population, although older children are more likely to experience nightmares (Beltrami and Hertzid, 1983).

III.I.5. School-age children (5 to 10 years)
Total sleep time shows a steady decline with increasing age but remains about 2.5 h longer than adult sleep time (Coble et al. 1987). By 10 years of life, children spend 8 to 10 h in bed and sleep approximately 95% of that time. Prepubescent preadolescents are alert throughout the day and rarely fall asleep (Carskadon et al. 1987). In this age range, daytime naps are rare (Carskadon et al. 1987). A minority of children nap at 5 and 6 years, and naps usually disappear by age 7. Sleep becomes quieter, and body movements decrease in frequency but are still more frequent than in older children. Difficulties in initiating and maintaining sleep are reported in about 4% of normal preadolescent children (Kahn et al. 1989).

III.I.6. Adolescents (11 to 18 years)

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As they mature, adolescents lose the ability to maintain adequate sleep, although they show no reduction of their "need" for sleep (Szymczak et al. 1993). There is a continuous decrease in total sleep time of about 2 to 3 h during adolescence, Time spent in bed and total sleep time decrease as the adolescents' age, resulting in a cumulative sleep debt. Prepubescent children average about 10 h a night, midadolescents 8.5 h, and older adolescents, primarily college students, about 7 h a night (Carskadon et al. 1987).

From 10 to 13 years of life, differences between weekend and school day sleep schedules progressively increase with age with girls presenting longer weekend time in bed and later weekend wake time than boys. The gender differences in adolescents' sleep patterns are most likely explained by the girls' higher pubertal status (Laberge et al. 2001). Whereas total sleep time for children 10 years of life tends to be the same on school nights as on non-school nights, young adolescents sleep about 40 min less during school nights than during non-school nights. The longer sleep time on non-school nights could reflect recovery from sleep deprivation during the week, as for school-age children bedtimes and wake times are controlled more by outside influences on school nights (Carskadon et al. 1980). Older adolescents report staying up to watch television or to do schoolwork on school nights and waking up by alarm in the morning. The demands of schoolwork escalate during adolescence, and parents tend to relinquish control of bedtime (Carskadon et al. 1987). Often subjective and objective evidence of increased daytime sleepiness appears. Older adolescents report greater difficulty with daytime sleepiness than do younger adolescents (Carskadon et al. 1987). Their sleepiness is most pronounced in the midafternoon (Carskadon et al. 1987).

III.II.   Sleep studies characteristics

III.II.1.   Preterm and term infants
The proportion of sleep stages changes over time: Active sleep constitutes 90% of sleep at 30 weeks' gestation and only 50% at term (Rigatto and Brady. 1972). On the EEG, Quiet sleep is formed by a combination of tracé alternant and high-voltage slow-wave near term. Tracé alternant which consists of long periods with low voltage activity interrupted by periods of irregular high delta and theta waves lasting up to 4 s, can be seen until 46 weeks' conceptional age. During the 2nd month after term, tracé alternant is progressively replaced by a sequence of EEG patterns corresponding to NREM stages.

III.II.2.   From birth to 12 months of life
During the first months of life, the infant's sleep characteristics shift to a more mature form. Quiet sleep progressively differentiates into four distinct stages (Hoppenbrouwers et al. 1982). On the EEG, the stage 1 is typified by bursts of high-voltage, rhythmic theta activity; sleep spindles and K complexes characterize the stage 2; and stages 3 and 4 contain slow, high-voltage delta waves. Stages 2, 3 and 4 EEG patterns occur only in NREM sleep stage, whereas the stage 1 EEG pattern can occur in wakefulness, REM sleep, and NREM sleep (Anders et al. 1971). The EEG characteristics of Quiet sleep change as the infant grows. So-called prespindles usually appear around 4 weeks of life and become fusiform by 6 weeks. Sleep spindles, a hallmark of stage 2, are seen by 6 months of age and reach synchrony by 18 to 24 months (Anders et al. 1971). Spindle density is maximal between 3 and 9 months of age and minimal between 27 and 54 months. Slow-wave delta activity appears at about 3 months of age (Coons and Guilleminault, 1982). K complexes, another hallmark of stage 2, appear at about 5

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months of life (Anders et al. 1971). Distinction between stages 3 and 4 becomes possible at 6 to 8 months. These stages are characterized by increasing proportions of slow, high-voltage, synchronous delta waves. Stages 3-4 NREM sleep is also known as "Slow-Wave" sleep, or "Delta sleep". These changes in NREM sleep have been linked with postnatal development of cortical control.

During sleep, REM and NREM states alternate. They follow each other in a periodic fashion and together compose a sleep cycle (Anders et al. 1971). The establishment of the periodic REM/NREM organization of sleep states is seen by 4 months of life (Harper et al. 1981). In the newborn, the duration of sleep cycles appear stable at 30 to 70 min. Throughout infancy and early childhood, sleep cycles' mean duration progressively lengthens to about 75 min. By midchildhood, these sequences gradually settle to about 90 min, as in adulthood.

In the first 6 months of life, REM sleep diminishes both in total time and its percentage of sleep time (Coons and Guilleminault, 1982). During the first months of life, REM sleep exceeds NREM sleep time. The amount of NREM sleep augments with age as that of REM sleep decreases. NREM sleep is the dominant sleep phase in 60% of infants at 3 months and in 90% of 6-month-old infants, when the proportion of NREM sleep is twice that of REM sleep. By 1 year of life, REM sleep occupies 40% of nighttime sleep (Anders et al. 1971).

Sleep-onset latencies are approximately 30 min at 2 months of age, 20 min at 6 months, and 15 min after 9 months. Throughout the first year of life, REM sleep latencies follow a bimodal distribution, with values of 8 min or less and 16 min or more. With increasing age, there is a shift to the longer latencies; REM sleep is seen in 64% of sleep onsets at 3 weeks of age and in 18% at 6 months (Coons and Guilleminault, 1987). By 3 months of age, a diurnal distribution of REM sleep latencies emerges, with the longest latencies measured between noon and 16:00 h and the shortest during the night.

III.II.3.   Preschool children (1 to 5 years)
Sleep-onset latency averages between 15 and 30 min in 1- to 5-year-old children. At sleep onset, NREM sleep predominates. Stage 2 NREM sleep appears within minutes after the child falls to sleep and stage 3 and 4 NREM sleep appear within 15 min after sleep onset.

The EEG elements and patterns continue to mature during the first 2 years of life. NREM sleep occurs mainly during the first third of the night, and slow-wave sleep density decreases across the night (Bes et al. 1991). As much as 2 h are spent in stages 3 and 4 NREM sleep. A gradual change is seen in the duration of the REM sleep periods. When the child is between 1 and 5 years of age, REM percentage gradually decreases from 30% of the total sleep time to the adult level of 20 to 25%. These changes are related to the augmented periods of daytime wakefulness. The first REM period occurs within 1 h after sleep onset. It is quite short, whereas succeeding periods tend to become longer and more intense by the end of the night.

Cycle lengths increase gradually from 40 min at 2 years of age to 60 min at 5 years of age. At this age, children have 7 to 10 cycles each nocturnal sleep period, with 3.5 stage shifts per hour.

III.II.4.   School-age children (5 to 10 years)

Mean sleep latencies exceed 15 min (Carskadon et al. 1987), with high between-subject variability (Coble et al. 1987). When the child is age 6 to 11 years, the volume of REM sleep remains relatively stable at 20 to 25% of sleep time (Coble et al. 1987). The proportion of stage 2 NREM sleep increases between 6 and 10 years of life and the amount of stage 4 NREM sleep decreases accordingly (Coble et al. 1987). The loss in stage 4 NREM sleep reaches 18% in 6- and 7-year-old children, an additional 14% in 10-year-old children and about 2 h in the latter portion of middle childhood (Carskadon et al. 1987).

III.II.5. Adolescents (11 to 18 years)
Polysomnographic characteristics have approximately normal young adult values, although body movements are occasionally seen more frequently than in adults. Slow-wave sleep decreases significantly in a linear fashion across the Tanner stages, with an approximately 35% decline from Tanner stage 1 (mean age 10.5 years) to Tanner stage 5 (mean age 16.9 years). The percentages of REM and NREM sleep now reach adult levels, and REM periods clearly lengthen as the sleep period progresses (Carskadon et al, 1980). Daytime alertness declines as adolescents grow. Their mean sleep-onset latency falls in mid-adolescence (Carskadon et al, 1987). More mature children are significantly sleepier at 13:30 h and 15:30 h than in the late afternoon and evening (Carskadon et al. 1980).

IV. Health consequences of sleep disturbances

Significant changes in performance and sleep physiology have been documented in adult subjects partially deprived of sleep (Sheldon et al. 1992). Total sleep deprivation studies in animals have shown significant deleterious effects (Sheldon et al. 1992). Experimental animals suffered severe pathological changes. Changes ranged from severely debilitated appearance (ungroomed and yellowed fur) to intense neurological abnormalities (ataxia and motor weakness) and death. In comparison, effects of total sleep deprivation on human subjects have been remarkably few. Although brief psychotic episodes have been reported in some adult subjects, long-term psychological effects do not appear. The only certain and reproducible effect of total sleep deprivation has been sleepiness, fatigue, decline in perceptual, cognitive and psychomotor capabilities, and increasing transient ego disruptive episodes (Sheldon et al.). As sleep deprivation continued up to 60 hours of continuous wakefulness, reality testing and performance became impaired and regressive behavior developed.

Children's response to acute restriction in sleep is similar to that in adults but shows some major differences. The effects of long-term sleep deprivation have been poorly studied in children.

IV.I   Factors that modify arousal thresholds in children.

Various factors may modify sleep and arousal characteristics, changing the child propensity to arouse or to maintain sleep. Endogenous factors that favor arousals from sleep include age, as arousal threshold decrease from birth to 4 months of life (Kahn et al. 1986); REM or NREM 2 sleep stage; duration of sleep (Rechschaffen et al. 1966); previous sleep deprivation (Franco et al. 2004); food allergy (Kahn et al. 1985); pain, stress or breathing problems (Rechschaffen et al. 1966). Environmental factors refer to ambient temperature (Franco et al. 2001), body position (Franco et al. 1998), beddings (Franco et al. 2002), drugs, exposure to cigarette smoke (Franco et al. 1999), or type of

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feeding (Franco et al. 2000). Ambient noise can also modify sleep-maintenance and arousal characteristics. In the literature, both short-term as well as medium-term effects of exposure to ambient stressors have been reported in children.

IV.II.   Sleep and arousal characteristics following a short sleep deprivation

The effects of short sleep deprivation on the following sleep periods were evaluated in 15 infants aged 78+/-7 days. Following a median sleep deprivation period of about 2 hours, the infants maintained a greater proportion of NREM sleep and had more frequent obstructive apnea (Canet et al. 1989; Thomas et al. 1996; Franco et al. in press). The results of these studies are in agreement with our findings in14 healthy 11-weeek-old infants, who were recorded before and following 2 h of sleep deprivation. Once sleep-deprived, the infants' respiratory changes were associated with significantly higher auditory arousal thresholds during REM sleep (Franco et al. in press) and increases in sympatho/vagal control of the heart rate (Franco et al. 2003).

The parents of 8.6-year old children (range 2 to 17 years) reported their child had difficult behaviors on the day that followed a 4-hour night-time sleep restriction (Wassmer et al. 1999). In a study, a 2-h sleep reduction induced by delayed bedtime, has been shown to increase daytime sleepiness, mainly during morning hours (Ishihara, 1999).

Daytime sleepiness has been reported to decrease with increasing age, while an afternoon dip occurs with pubertal development (Ishihara 1998). Following one night of 4 h of sleep deprivation imposed on children (aged 11 to 13 years), a decrease in performance tests has been observed (Carskadon et al. 1981). These children, however, showed no significant change in addition, attention or memory tests, despite a significant increase in daytime sleepiness (Carskadon et al. 1981,b).

In another set of experiments, following one-night sleep loss, adolescents showed increased sleepiness, fatigue, and reaction time. They selected less difficult academic tasks during a set of tests, but the percentages of correct responses were comparable to those seen following a normal sleep night (Engle-Friedman et al. 2003).

Another study has been conducted on 82 children, 8 to 15 years of age. They were assigned an optimised, 10-hour night of sleep, or a restricted 4-hour night of sleep. Sleep restriction was associated with shorter daytime sleep latency, increased subjective sleepiness, and increased sleepy and inattentive behaviors, but was not associated with increased hyperactive-impulsive behavior or impaired performance on tests of response inhibition and sustained attention (Fallone et al. 2001).

IV.III.   Behavior, school and learning performances following repeated sleep deprivation

Although children appear to tolerate a single night of restricted sleep without a decrement in performance on brief tasks, perhaps more prolonged restriction and prolonged tasks similar to those required in school would show decrement. In addition, as children seem to require more time to recuperate fully from nocturnal sleep restriction than adults (Carskadon et al. 1981), with additional nights of partial sleep deprivation, cumulative sleepiness might become a significant problem.

Empirical data that directly addresses the effects of repeated sleep loss on children's mood or cognitive function are sparse. A range of clinical and observational data support

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a general picture that inadequate sleep results in tiredness, difficulties with focussed attention, low thresholds to express negative affects (irritability and easy frustration), as well as difficulty in modulating impulses and emotions. In some cases, these symptoms resemble attention deficit hyperactivity disorder.

At 3 years of age children with persistent sleep problems (n= 308) were more likely to have behavior problems, especially tantrums and behavior management problems (Zuckerman et al. 1987).

In a study on16 children with a mean age of 12+/- 4 years, suffering from chronic pain due to juvenile rheumatoid arthritis and secondary poor sleep, polysomnographic recordings showed more night-time poor sleep, longer afternoon naptime and more Zuckerman, than normal values from the literature (Zamir et al. 1998).

In a school survey, among 9 to 12 year old children (n= 1000), those with poor sleep (insomnia for more than 6 months) had poorer school performance, defined as failure to comply with expected grades, than good sleepers. Their learning problems were tentatively attributed to the long-term effect of poor sleep (Kahn et al. 1989).

A questionnaire administered on 4- to12 year-old children (n= 472) showed a relation between sleep problems and tiredness during the day (Stein et al. 2001).

In 9 to 12 year-old children (n= 77), shortening sleep by one hour was associated with reduced alertness and significant lowering of neurobehavioral functioning (Sadeh et al. 2003). In school-age children (n= 140) recorded at home with an actigraph, a significant relation was shown between the presences of fragmented sleep, daytime sleepiness and lower performance on neurobehavioral functioning evaluated by various performance tests (Sadeh et al. 2000). These children also had higher rates of behavior problems, as reported by their parents (Sadeh et al. 2002).

In Finland, children, aged 7 to 12 years (n= 49), were interviewed together with their parents and schoolteachers and recorded for 72 h with a belt-worn activity monitor during weekdays. The decreased amount of sleep was associated with symptoms, such as aggressive and delinquent behavior, attention, social, and somatic problems. The sleep findings were better associated with the teachers' than the parents reports, suggesting that parents may be unaware of their child's sleep deficiencies as the behavioral problems may be more evident at school than at home (Aronen et al. 2000).

A prospective long-term study on 2518 children conducted in Sweden, revealed that within a subgroup of 27 children with severe and chronic sleep problems, 7 children developed symptoms that met the criteria for attention-deficit/hyperactivity disorder by the age of 5.5 years (Thunström, 2002). Compared to the other children with sleep problems, these subjects had more frequent psychosocial problems in the family, bedtime struggles and long sleep latency at bedtime.
A questionnaire population-based, cross-sectional survey has been conducted in Massachusetts on 30195 children, aged 5 years (Gottlieb et al. 2003). Children described by their parents with sleep-disordered breathing (snoring, noisy breathing, apnea) were significantly more likely to have daytime sleepiness and problem behaviors, including hyperactivity, inattention and aggressiveness (all with odds ratio > 2.0). These problem behaviors were suggestive of attention-deficit/hyperactivity disorder.

Similar findings were found in a group of 5 to 7 year-old children with periodic limb movement disorder were studied polygraphically and their recording compared with those of age-matched children with attention-deficit/hyperactivity disorder. Their repeated sleep fragmentation resulting from the periodic limb movement disorder favored the development of symptoms similar to those seen in the attention-deficit/hyperactivity disorder (Crabtree et al. 2003).

IV.IV.   Other health-related effects

IV.IV.1.   Depression

Depressed children and adolescents exhibit less sleep continuity and Non-REM sleep than control subjects (Emslie et al. 2001). Abnormal sleep studies were reported to predict recurrence of depressive symptoms in children and adolescents (Emslie et al. 2001). Children with trouble sleeping had significantly increased odds of anxiety/depression based on mothers' reports; the association increased from 6 to 11 years of life (Johnson et al. 2000).

An unexpectedly high proportion of children between 14 and 17 years of age with poor sleep have been shown to suffer of moderate to severe depression (Manni et al. 1997; Ohayon et al. 1997; Vandeputte and de Weerd, 2003). A group of 4175 adolescents, 11 to 17 years of age, were followed-up for one year. The study showed that insomniac adolescents developed impaired daytime functioning and depressive feelings (Roberts et al. 2002).

It is not known, however, how sleep and mood disorders are associated in children. In a study on the association between maternal depression and persistent sleep problems in 3 to 4 year-old children, the children's and mother's depressive symptoms appeared to result from, rather than to cause the sleep problems (Lam et al. 2003).

In a longitudinal 4-year survey on 7960 adolescents, 12 to 18 years old, depressive symptoms preceded the development of sleep problems (Patten et al. 2000). In 569 schoolchildren, with mean ages from 10 to 15 years, a strong association between the report of physical pain, mental distress and sleep problems was found, however, the complaints could represent simultaneous signs of a multi symptom syndrome (Bruusgaard et al. 2000).

Among 490 children followed-up from age 4 to 15 years, a progressively increased correlation was found between sleep problems and depression/anxiety. It was concluded that if early sleep problems may forecast emotional problems, important developmental change exist in the overlap between sleep problems and emotional problems (Gregory and O'Connor, 2002). Available evidence thus appears to suggest that prolonged poor sleep can cause or aggravate mood depression in children. The issue is, however, complex as both sleep and mood problems are interrelated and may depend on a common susceptibility.

IV.IV.2.   Weight excess

In a questionnaire survey conducted in Japan on 8274 children, aged 6 to 7 years, there was a significant dose-response relationship between short sleeping hours and childhood obesity (Sekine et al. 2002). The association could reflect a relation between short sleeping hours, increased sympathetic activity, elevated cortisol secretion and

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decreased glucose tolerance (Spiegel et al. 1999). No objective data are available, however, to confirm such association. In addition, there are no data in the pediatric literature to sustain the existence of sleep-related eating disorders, as seen in adult patients with excessive eating habits secondary to sleep disorders (Schenck et al. 1991).

The relation between sleep loss and weight excess is complex. It was shown that if 11-16 years old adolescents experienced less sleep than non-obese adolescents, sleep disturbances influenced a decrease in physical activity level, but were not directly related to obesity, but (Gupta et al. 2002). In a sleep study, we could show that overweight infants have alterations in sleep stages and suffer from repeated upper airway obstruction, that may aggravate poor sleep at night and increase daytime sleepiness (Kahn et al. 1989,b). Likewise, rapid weight loss in adolescents with morbid obesity induce a decrease in sleep abnormalities (Willi et al. 1998).

IV.IV.3.   Parasomnia

Parasomnia are sleep-wake transition disorders. Sleep debt elevates arousal thresholds and could hence favor the development of parasomnia in children, such as sleepwalking, sleep terrors or enuresis (Mehlenbeck et al. 2000).

IV.IV.4.   Seizures

Sleep deprivation activates epileptic discharges independent of the activating effect of sleep. Techniques to induce sleep restriction have been advocated for the identification of seizure in children (Liamsuwan et al. 2000). However, the induction of sleep deprivation in 8-year old children has been reported to be poorly accepted by both parents and children, and the efficiency of the technique may be low (Wassmer et al. 1999).

IV.IV.5.   Cardiovascular changes

No data is available in children on the potential development of cardiovascular problems secondary to prolonged poor sleep. It is not known whether chronically sleep-deprived children develop hypertension or abnormal cardiac function because of secondary autonomic changes. In 3 month-old infants deprived of two hours of sleep, an increase in sympathetic control of the heart rate has been measured (Franco et al. 2003). One night sleep deprivation in young men, aged 18 to 27 years, has been associated with increases in both sympathetic activity and cortisol concentrations (Spiegel et al. 1999).

IV.IV.6.   The immune system

Little is known on the effects of sleep deprivation on the immune system in children. Observations have associated the development of infections to sleep deficiency and fatigue. In young volunteers, 24 hours sleep deprivation was associated with a significant reduction in lymphocyte chemotaxis to chemotactic factors (Matsui et al. 1991). The findings were interpreted as showing that fatigue due to sleep deprivation plays a major role in the susceptibility to acute infections.

IV.IV.7.   Carbohydrate metabolism and endocrine function

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Sleep deprivation in young men, aged 18 to 27 years, has been associated with elevated cortisol and thyrotropin concentrations together with a decreased glucose tolerance (Spiegel et al. 1999).

IV.IV.8. Accidents

In a study including adolescents over 15 years and adults, twice as many subjects operating a motor vehicle or using machine tools reported having a crash or accident in the previous year, than did the general population with no daytime sleepiness (Ohayon et al. 1997).

IV.IV.9 Medications, alcohol, cigarettes and drugs

Sleep deprivation and associated day-time fatigue could induce coping strategies that include the use of short- and long-term use sleep-inducing drugs as well as of excitatory substances, such as smoking or caffeine. These medications could induce unwanted health effects.

In a survey of 9 to 12 year-old children (n= 972), conducted in Belgium, regular use of sedative drugs was found in 4% of the 132 children who slept poorly (Kahn et al. 1989). The same frequency of sleep promoting drugs use, including benzodiazepines, was reported in a group of 17-year-old adolescents from Italy (Manni et al. et al. 1997).
In a survey on 13831 adolescents, an association was found between sleep problems and use of illicit drugs (Johnson and Breslau, 2001). In another study including adolescents over 15 years of age and adults, severe daytime sleepiness was associated with high daily caffeine consumption (Ohayon et al. 1997).

The reasons for these associations remain unknown. Common factors could relate poor sleep and the use of excitatory substances or nicotine. In a prospective survey on 12 to 18 year-old adolescents, cigarette smoking status showed a dose-response relationship with the development of sleep problems (Patten et al. 2000). In this study, cigarette smoking was strongly associated with children's reports of anxiety/depression. In another study on high school students, smoking habits was reported to induce or aggravate sleep disturbance (Phillips and Danner, 1995). Further prospective studies should be conducted to determine whether prolonged sleep deprivation favors the consumption of cigarettes, alcohol or illicit drugs in adolescents.

IV.IV.10. The Sudden infant Death syndrome

The ability to arouse from represents a survival response in life-threatening conditions, such as airway obstruction during sleep (Bowes et al. 1980). Insufficient and incomplete arousal responses have been shown in infants victims of the Sudden Infant Death syndrome (Kato et al. 2003). Such failure to arouse could be enhanced by previous sleep deprivation, as sleep-deprived infants have higher arousal thresholds during the following sleep period (Franco et al. in press).

V . Conclusions (Table II).

Although short-term effects of sleep deprivation in school-age children appear to be manifested by daytime fatigue only, medium-term effects have been associated with

daytime sleepiness and problem behaviors suggestive of attention-deficit/hyperactivity disorder.

Several limitations to the present report should be discussed. Firstly, we do not know whether the inference that is often made that the effects of ambient stressors might develop with a longer exposure time is correct. Serious cardiorespiratory or autonomic changes, such as increases in blood pressure could only develop following long-time exposure starting from childhood. This, in fact, has never been documented, nor has the extent of inter-subject variability, due to differences in susceptibility.

Secondly, we have no information to evaluate whether adaptation to sleep deprivation could limit its effects observed during short- and medium-term experiments.
Finally, as the existing research data are applicable to generally healthy children, we do not know how the reported findings could be applied to ill children, children receiving medical treatments or very young premature infants.

Despite these limitations, it can be concluded that, based on the available evidence, repeated or chronic sleep disruption in children could be pervasive, effecting the children's physical, mood and cognitive well being. Changes in sleep quantity and quality together with autonomic reactions are seen during exposure to ambient stressors during sleep, reflecting modifications within the brain of the sleeping child. It remains, however, to be determined what long-term effects pervasive ambient stressors have on the child's cognitive, mood and physical development.

The multifactor effects of environment on sleep and arousal controls could be much more complex than expected. On might predict that the effects of sleep deprivation on the child's sleep and health depend upon the stressor responsible for the deprivation or fragmentation of sleep, temporal aspects of the stressor, genetic predisposition, psychological responses to the stressor, and the nature as well as the duration of the evaluation.

VI.   Future research topics

Important aspects of the responses of sleeping children to environmental stressors and the resulting sleep deprivation need further evaluation. Studies are particularly needed in children to determine cause and effect relationships for most health effects associated with sleep deprivation. Some of the potentials for further researches are summarized as follows:
There is interest in the collection of experimental data on the effects of sleep fragmentation and deprivation at different age groups (Wesensten et al. 1999).
Following preliminary observations in animal studies (Bowes et al. 1980), arousal responses to laryngeal and respiratory stimuli should be studied following both sleep fragmentation and deprivation.
The potential effects of sleep deprivation on children's immune system should be evaluated (Mullington and al. 1997).
The relation between sleep debt and carbohydrate metabolism and endocrine function should be evaluated in children (Spiegel et al. 1999).
Arousal thresholds should be re-evaluated with the use of computer-based algorithms, and techniques such as non-linear dynamics of the waking EEG (Jeong et al. 2001).
The determination of usual coping strategies, including the use of short- and long-term use of sleep-inducing or excitatory drugs, should be studied in children.

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The evaluation of the long-term effects of sleep deprivation in children should be conducted during adult life.

VII. References

Anders T, Emde R, Parmelee AH, eds. 1971. A manual of standardized terminology, techniques and criteria for scoring states of sleep and wakefulness in newborn infants. Los Angeles: UCLA Brain Information Service, NINDS Neurological Information Network.

Anders TF, Keener M. 1985. Developmental course of nighttime sleep-wake patterns in full-term and premature infants during the first year of life. I. Sleep 8:173-192.

Aronen ET, Paavonen EJ, Fjällberg M, Soininen M, Törrönen J. 2000. Sleep and psychiatric symptoms in school-age children. Journal of the American Academy of Childhood and Adolescent Psychiatry 39:502-508.

Beltrami AU, Hertzid ME. 1983. Sleep and bedtime behavior in preschool-aged children. Pediatrics 71:153-158.

Berstein P, Emde R, Camps J. 1973. REM sleep in four-month infants under home and laboratory conditions. Psychosomatic Medicine 35:322-329.

Bes F, Schulz H, Navelet Y, Salzarulo P. 1991. The distribution of slow-wave sleep across the night : a comparison for infants, children and adults. Sleep 14:5-12.

Bowes G, Woolf GM, Sullivan CE, Phillipson EA. 1980. Effects of sleep fragmentation in ventilatory and arousal responses of sleeping dogs to respiratory stimuli. American Review of Respiratory Disease 122:899-908.

Brouillette RT. 1992. Assessing cardiopulmonary function during sleep in infants and children. In: Beckerman RC, Brouillette RT, Hunt CE, eds. Respiratory control disorders in infants and children. Baltimore: Williams and Wilkins 125-141.

Bruusgaard D, Smedbraten BK, Natvig B. 2000. Bodily pain, sleep problems and mental distress in schoolchildren. Acta Paediatrica 89;597-600.

Canet E, Gaultier C, D'Allest A. 1989. Effects of sleep deprivation on respiratory events during sleep in healthy infants. Journal of Applied Physiology 66:1158-1163.

Carskadon MA, Harvey K, Duke P, Anders FA, Lit IF, Dement WC. 1980. Pubertal changes in daytime sleepiness. Sleep 2:453-460.

Carskadon MA, Harvey K, Dement WC. 1981. Sleep loss in young adolescents. Sleep 4:299-321.

Carskadon MA, Harvey K, Dement WC. 1981. Acute restriction of nocturnal sleep in children. Percept Motor Skills 53:103-112 (b).

Carskadon MA, Keenan S, Dement WC. 1987. Night-time sleep and day-time sleep tendency in preadolescents. In: Guilleminault C, ed. Sleep and its disorders in children. New York: Raven Press 43-52.

Coble PA, Kupfer DJ, Reynolds III CF, Houck P. 1987. EEG sleep of healthy children 6 to 12 years of age. In: Guilleminault C, ed. Sleep and its disorders in children. New York: Raven Press 29-41.

Committee on Environment Health of the American Academy of Pediatrics. 1997. Noise: a hazard for the fetus and newborn. Pediatrics 100:724-727.

Coons S, Guilleminault C. 1982. Development of sleep-wake patterns and non-rapid eye movements sleep stages during the first six months of life in normal infants. Pediatrics 69:793-798.

Crabtree VM, Ivanenko A, O'Brien LM, Gozal D. 2003. Periodic limb movement disorder of sleep in children. Journal of Sleep Research 12:73-81.

Curzi-Dascalova L, Lebrun F, Korn G. 1983. Respiratory frequency according to sleep states and age in normal premature infants: a comparison with full-term infants. Pediatric Research 17:152-156.

Curzi-Dascalova L, Mirmiran M. 1996. Manual of methods for recording and analyzing sleep-wakefulness states in perterm and full-term infant. INSERM edit. Paris, France.

Dawes GS, Fox HE, Leduc BM, Liggins GC, Richards RT. 1972. Respiratory movements and rapid eye movement sleep in the foetal lamb. Journal of Physiology 220:119-193.

Emde RN, Walker S. 1976. Longitudinal study of infant sleep: results of fourteen subjects studied at monthly intervals. Psychophysiology 13:546-461.

Emslie GJ, Armitage R, Weinberg WA, Rush AJ, Mayes TL, Hoffmann RF. 2001. Sleep polysomnography as a predictor of recurrence in children and adolescents with major depressive disorder. International Journal of Neuropsychopharmacology 4:159-168.

Engle-Friedman M, Riela S, Golan R, Ventuneac AM, Davis CM, Jefferson AD, Major D. 2003. The effect of sleep loss on next day effort. Journal of Sleep Research 12:113-124.

Fallone G, Acebo C, Arnedt JT, Seifer R, Carskadon MA. 2001. Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. Perceptual and Motor Skills 93:213-229.

Flores-Guevara R. 1987. Night-to-night variability of sleep respiratory pauses in normal infants. Neuropediatrics. 18:196-199.

Fountain NB, Kim JS, Lee SI. 1998. Sleep deprivation activates epileptiform discharges independent of the activating effects of sleep. Journal of Clinical Neurophysiology 15:69-75.

Franco P, Pardou A, Hassid S, P Lurquin, Kahn A. 1998. Auditory arousal thresholds are higher when infants sleep in the prone position. Journal of Pediatrics 132:240-3.

Franco P, Groswasser J, Hassid S, Lanquart JP, Scaillet S, Kahn A. 1999. Prenatal exposure to cigarettes is associated with decreased arousal propensity in infants. Journal of Pediatrics 135:34-8.

Franco P, Scaillet S, Wermenbol V, Valente F, Groswasser J, Kahn A. 2000. The influence of a pacifier on infants' arousals from sleep. Journal of Pediatrics 136:775-779.

Franco P, Scaillet S, Valente F, Chabanski S, Groswasser J, Kahn A. 2001. Ambient temperature is associated with changes in infants'arousability form sleep. Sleep 24:325-329.

Franco P, Lipshutz W, Valente F, Adams S, Scaillet S, Groswasser J, Kahn A. 2002. Decreased arousals in infants sleeping with the face covered by bedclothes. Pediatrics 109:112-117.

Franco P, Seret N, Van Haas JN, Lanquart JP, Groswasser J, Kahn A. 2003. Cardiac autonomic changes during sleep in sleep-deprived infants. Sleep 26:845-851.

Franco P, Seret N, Van Hees JN, Scaillet S, Vermeulen F, Groswasser J, Kahn A. 2004. Decreased arousals in healthy infants following short-term sleep deprivation. Sleep (in press).

Gaultier C.1987. Respiratory adaptation during sleep from the neonatal period to adolescence. In: Guilleminault C, ed. Sleep and its disorder in children. New York: Raven Press 67-98.

Guilleminault C, Souquet M. 1979. Sleep states and related pathology. In: Korobkin R, Guilleminault C, eds. Advances in perinatal neurology. New York: Spectrum Publications 225-247.

Gottlieb DJ, Vezina RM, Chase C, Lesko SM, Heeren TC, Weese-Mayer DE, Auerbach SH, Corwin MJ. 2003. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics 112:870-877.

Gergory AM, O'Connor TG. 2002. Sleep problems in childhood: a longitudinal study of developmental change and assciation with behavioural problems. Journal of the American Academy of Child and Adolescent Psychiatry 41:964-971.

Gupta NK, Mueller WH, Chan W, Meininger JC. 2002. Is obesity associated with poor sleep quality in adolscents ? American Journal of Human Biology 14:762-768.

Haddad GG, Jung HJ, Lai TL, Mellins RB. 1987. Determination of sleep state in infants using respiratory variability. Pediatric Research. 21:556-562.

Harper RM, Leake B, Miyahara L, Hoppenbrouwers, Sterman MB, Hodgman J. 1981. Temporal sequencing in sleep and waking states during the first 6 months of life. Experimental Neurology 72:294-307.

Hoppenbrouwers T, Ugartechea JC, Combs D, Hodgman JE, Harper RM, Sterman MB. 1978. Studies of maternal-fetal interaction during the third trimester of pregnancy. I. Ontogenesis of the basic rest activity cycle. Experimental Neurology 136-153.

Hoppenbrouwers T, Jensen DK, Hodgman GE, Harper RM, Sterman MB. 1979. Respiration during the first six months of life in normal infants. II. The emergence of a circadian pattern. Neuropediatrie. 10:264-280.

Hoppenbrouwers T, Hodgman JE, Harper RM, Sterman MB. 1982. Temporal distribution of sleep states, somatic activity during the first half year of life. Sleep 5:131-144.

Iglowstein I, Jenni OG, Molinari L, Largo RH. 2003. Sleep duration from infancy to adolescents: reference values and generational trends. Pediatrics 111:302-307.

Ishihara K, Miyke S. 1998. A longitudinal study of the development of daytime sleepiness in children. Psychiatry and Clinical Neurosciences 52:178-181.

Ishihara K. 1999. The effect of 2-h sleep reduction by a delayed bedtime on daytime sleepiness in children. Psychiatry and Clinical Neurosciences 53:113-115.

Jeong J, Kim DJ, Kim SY, Chae JH, Go HJ, Kim KS. 2001. Effect of total sleep deprivation on the dimensional complexity of the waking EEG. Sleep 24:197-202.

Johnson EO, Chilcoat HD, Breslau N. 2000. Trouble sleeping and anxiety/depression in chilhood. Psychiatry Research 94:93-102.

Johnson EO, Breslau N. 2001. Sleep problems and substance use in adolescence. Drug and Alcohol Dependence 64:1-7.

Kahn A, Mozin MJ, Casimir G, Montauk L, Blum D. 1985. Insomnia and cow's milk allergy in infants. Pediatrics 76:880-884.

Kahn A, Picard E, Blum D. 1986. Auditory arousal thresholds of normal and near-miss SIDS infants. Developmental Medicine and Child Neurology 28:299-302.

Kahn A, Van de Merckt, Rebuffat E, Mozin MJ, Sottiaux M, Blum D, Hennart P. 1989. Sleep problems in healthy preadolescents. Pediatrics 84 : 542 - 546.

Kahn A, Mozin MJ, Rebuffat E, Sottiaux M, Burniat W, Shepherd S, Muller MF. 1989 b. Sleep pattern alterations and brief airway obstructions in overweight infants. Sleep 12:430-438.

Kahn A, Dan B, Groswasser J, Franco P, Sottiaux M. 1996. Normal sleep architecture in infants and children. Journal of Clinical Neurophysiology 13:184-197.

Kahn A, Franco P, Groswasser J, Scaillet S, Kelmanson I, Kato I, Dan B. 2002. Noise exposure from various sources: sleep disturbance, dose-effect relationships on children. WHO, Bonn, September Technical meeting. http://www.euro.who.int/noise. 2002.

Kato I. Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, Kahn A. 2003. Incomplete arousal processes in infants with sudden death. American Journal of Respiratory and Critical Care 164:1464-1469.

Katona PG, Frasz A, Egbert J. 1980. Maturation of cardiac control in fullterm and preterm infants during sleep. Early Human Development 472:145-159.

Kohler WC, Coddington D, Agnew HW. 1968. Sleep patterns in 2 year-old children. Journal of Pediatrics 72:228-233.

Laberge L, Petit D, Simard C, Vitaro F, Tremblay RE, Montplaisir J. 2001. Development of sleep patterns in early adolescence. Journal of Sleep Research 10:59-67.

Lam P, Hiscock H, Wake M. 2003. Outcomes of infant sleep problems: a longitudinal study of sleep, behavior, and maternal well-being. Pedaitrics 111:e203-207.

Liamsuwan S, Grattan-Smith P, Fagan E, Bleasel A, Antony J. 2000. The value of partial sleep deprivation as a routine measure in pediatric electroencephalography. Journal of Child Neurology 15:26-29.

Manni R, Rattli MT, Marchioni E, Castelnovo G, Murelli R, Sartori I, Galimberti CA, Tartara A. 1997. Poor sleep in adolescents: a study of 869 17-year-old Italian secondary school students. Journal of Sleep Research 6:44-49.

Matsui Y, Saito K, Nakakuma T, Michi K. 1991. Studies on the host factors in the outbreak of ondontogenic infection – the background factors of patines and the effects of serum after sleep deprivation on PMN chemotaxis. Kansenshogaku-Zasshi 65:47-53.

Mehlenbeck R, Spirito A, Owens J, Boerges J. 2000. The clinical presentation of childhood partial arousal parasomnias. Sleep Medicine 1:307-312.

Mullington J, Hinze-Selch D, Fenzel T, Korth DHC, Pollmächer T. 1997. A sleep deficit leads to a blunting of the pyrogenic response to endotoxin in healthy men. Sleep 21s:10.

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Nijhuis JG, Prechtl HRF, Martin CB, Bots RSGM. 1982. Are there behavioural states in the human fetus ? Early Human Development 6:177-195.

Ohayon MM, Caulet M, Philip P, Guilleminault C, Priest RG. 1997. How sleep and mental disorders are related to complaints of daytime sleepiness. Archives of Internal Medicine 157:2645-2652.

Parmelee AH, Wenner WH, Akiyama Y. 1967. Sleep states in premature infants. Development Medicine and Child Neurology 9:70-77.

Parmelee AH, Stern E, Harris MA. 1972. Maturation of respiration in prematures and young infants. Neuropaediatric 3:294-304.

Patten CA, Choi WS, Gillin JC, Pierce JP. 2000. Depressive symptoms and cigarette smoking predict development and persistence of sleep problems in US adolescents. Pediatrics 106: E23.

Phillips BA, Danner FJ. 1995. Cigarette smoking and sleep disturbance. Archives of Internal Medicine 155:734-737.

Prechtl HFR. The behavioural states of the newborn infant (A review). 1974. Brain Research 76:185-212.

Rechtschaffen A, Hauri P, Zeitlin M. 1966. Auditory awakening thresholds in REM and NREM sleep stages. Perceptual and Motor Skills 22:927-942.

Reite M, Buysse D, Reynolds C, Mendelson W. 1995. The use of polysomnography in the evaluation of insomnia. An American Sleep Disorder Association review. Sleep 18:58-70.

Rigatto H, Brady JP. 1972. Periodic breathing and apnea in preterm infants. II. Hypoxia as a primary event. Pediatrics 50:219-228.

Roberts RE, Roberts CR, Chen IG. 2002. Impact of insomnia on future functioning of adolescents. Journal of Psychosomatic Research 53:561-569.

Sadeh A, Raviv A, Gruber R. 2000. Sleep patterns and sleep disruptions in school-age children. Developmental Psychology 36:291-301.

Sadeh A, Gruber R, Raviv A. 2002. Sleep, neurobehavioral functioning, and behavior problems in school-age children. Child Development 73:405-417.

Sadeh A, Gruber R, Raviv A. 2003. The effects of sleep restriction and extension on school-age children: what a difference an hour makes. Child Development 74:444-455.

Schenck CH, Hurwitz TD, Bundlie SR, Mahowald MW. 1991. Sleep-related eating disorders: polysomnographic correlates of a heterogeneous syndrome distinct form daytime eating disorders. Sleep 14:419-431.

Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, Tokui N, Yoshida K, Kagamimori S. 2002. A dose-response relationship between short sleeping hours and childhood obesity: results of the Toyama birth cohort study. Children Care and Health Development 28:163-170.

Sheldon SH, Spire JP, Levy HB. 1992. Pediatric Sleep Medicine. Saunders WB. Philadelphia 1-13.

Spiegel K, Leproult R, Van Cauter E. 1999. Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435-1439.

Stein MA, Mendelsohn J, Obermeyer WH, Amromin J, Benca R. 2001. Sleep and behavior problems in school-aged children. Pediatrics 107:766 (e).

Sterman MB, Hoppenbrouwers T. 1971. The development of sleep-waking and rest-activity patterns from fetus to adult in man. In: Sterman MB, McGinty DJ, Adinofi AM, eds. Brain development and behavior. New York: Academic Press 203-225.

Szymczak JT, Jasinska M, Pawlak E, Zwierzykowska M. 1993. Annual and weekly changes in the sleep-wake rhythm of school children. Sleep 16:433-435.

Thomas DA, Poole K, McArdle EK, Goodenough PC, Thompson J, Beardsmore CS, Simpson H. 1996. The effect of sleep deprivation on sleep states, breathing events, peripheral chemosensiveness and arousal propensity in healthy 3 month old infants. European Respiratory Journal 9:932-938.

Thunström M. 2002. Severe sleep problems in infancy associated with subsequent development of attention-deficit/hyperactivity disorder at 5.5 years of age. Acta Paediatrica 31:584-592.

Vandeputte M, de Weerd A. 2003. Sleep disorders and depressive feelings: a global survey with the Beck depression scale. Sleep Medicine 4:343-345.

Wassmer E, Quinn E, Seri S, Whitehouse W. 1999. The acceptability of sleep-deprived electroencephalograms. Seizure 8:434-435.

Wesensten NJ, Balkin TJ, Belenky G. 1999. Doses sleep fragmentation impact recuperation ? A review and reanalysis. Journal of Sleep Research 8:237-245.

Willi SM, Oexmann MJ, Wright JM, Collop NA, Key LLJ. 1998. The effects of a high-protein, low-fat, ketogenic diet on adolescents with morbid obesity: body composition, blood chemistries, and sleep abnormalities. Pediatrics 101:61-67.

Zamir G, Press J, Tal A, Tarasiuk A. 1998. Sleep fragmentation in children with juvenile rheumatoid arthritis. Journal of Rheumatology 25:1191-1197.

Zuckerman B, Stevenson J, Bailey V. 1987. Sleep problems in early childhood: continuities, predictive factors, and behavioural correlates. Pediatrics 80:664-671.

TABLE I   Usual sleep duration according to age

AGE	Sleep Duration	Authors
Fetus		
30 wk	53% of time	Parmelee et al. 1967
40 wk	60%	Sterman and Hoppenbrouwers, 1971
Infant		
0-1 m	16-17 h	Parmelee et al. 1967
1.5 m	14-15 h	
6 m	13-14 h	
Child		
1 year	14-45 h	Parmelee et al. 1967
2 years	13-14 h	Kohler et al. 1968
4 years	12-13 h	
10 years	8-10 h	Carskadon et al. 1987
Adolescent		
12 years	8- 9 h	
18 years	7- 8 h	

TABLE II   Effects of sleep deprivation in children

A) Effects of short term sleep deprivation

Behavioral	Daytime fatigue Decreased performance and concentration, memory difficulties Difficult behaviors
Medical	Undetermined
Mortality	Increased risk (Sudden Infant Death syndrome) ?

B) Effects of repeated sleep deprivation

Behavioral	Difficulty in modulating impulses and emotions. Poor performance at school, fatigue, memory difficulties, concentration problems. Increased risk of accidents ?
Psychiatric	Depression, anxiety conditions ? Aggressive and delinquent behavior ? Attention-deficit/hyperactivity disorder ? Alcohol, smoking, caffeine and other substance abuse ?
Medical	Increases in sleep disorders (parasomnia) Increased risk of obesity ? Changes in carbohydrate metabolism ? Changes in immune system ?
Mortality	Increased risk (Sudden Infant Death syndrome) ?

Sleep disorders in adults ; biological mechanisms through which sleep disorders affect the health of adults. Identification of environmental factors leading to clinical sleep disorders - Michel Billiard

Michel Billiard M.D.
Professor of Neurology
Department of Neurology
Gui de Chauliac Hospital
34295, Montpellier, cedex 5
France

Phone : (33) 4 67 02 11 54

Fax : (33) 4 67 66 18 62

E-mail : mbilliard@wanadoo.fr

Summary

According to the Diagnostic and Statistical Manual of Mental Disorders (1) there are four categories of sleep disorders, primary sleep disorders including dyssomnias and parasomnias ; sleep disorders related to another mental disorder including insomnia and hypersomnia related to another mental disorder ; and other sleep disorders including sleep disorders due to a general medical condition or a substance induced sleep disorder. The current presentation focuses on five distinct sleep disorders, all listed in the category of dyssomnias and all presenting with repeated interruptions of sleep, namely primary insomnia, narcolepsy, breathing related sleep disorders, environmental sleep disorder and periodic leg movement sleep disorder (PLMD). All these disorders belong to the category of dyssomnias. Definition, prevalence, clinical features, diagnostic tests are briefly outlined while biological mechanisms by which these sleep disorders may affect health of patients are more thorougly considered. Importance of environmental factors differs widely according to these disorders

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (1) there are four categories of sleep disorders, primary sleep disorders including dyssomnias and parasomnias ; sleep disorders related to another mental disorder including insomnia and hypersomnia related to another mental disorder ; and other sleep disorders including sleep disorders due to a general medical condition or a substance induced sleep disorder. The current presentation focuses on five distinct sleep disorders, all listed in the category of dyssomnias and all presenting with repeated interruptions of sleep, namely primary insomnia, narcolepsy, breathing related sleep disorders, environmental sleep disorder and periodic leg movement sleep disorder (PLMD), with the emphasis put on the biological mechanisms through which sleep disorders affect the health of adults. The ultimate goal of the presentation is to make noise specialists familiar with the inner mechanisms of various sleep disorders, with the hope that they shed some light on the mechanisms by which night noise may impact on adult health.

Primary insomnia

Definition

Primary insomnia is characterized by a complaint of difficulty falling asleep or maintaining sleep or of non restorative sleep, which is responsible for an alteration of social and other domains of functioning. The alteration of sleep does not exclusively occur in the context of another sleep disorder, a psychiatric disorder or the intake of a substance (1).

Prevalence

In sleep disorders centers about 15 to 25% of subjects complaining of chronic insomnia insomniacs receive a diagnosis of primary insomnia (1)

Clinical features

Individuals presenting with primary insomnia often complain of difficulties initiating sleep or maintaining sleep. Less often they may only complain of non restorative sleep, that is agitated, light or poor sleep. Primary insomnia develops as a consequence of two mutually reinforcing factors : somatized tension and learned sleep-preventing associations.
Individuals with primary insomnia typically react to stress with somatized tension and agitation. Learned sleep-preventing associations can be due either to internal cognitions or to external stimuli. Learned internal associations consit mainly of a marked overconcern with the inability to sleep. A vicious cercle then develops : the more one strives to sleep, the more agitated one becomes, and the less, then, one is able to fall asleep. Patients in whom this internal factor (trying too hard to sleep) is a driving force for insomnia often find that they fall asleep easily when not trying to do so, e.g. while watching television, reading, or driving. Conditioned external factors causing insomnia often develop from the continued association of sleeplessness with situations and behaviors that are related to sleep. Thus , just lying in a bedroom in which one has frequently spent sleepless nights may cause conditioned arousal, as may behaviors that

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lead up to frustration of not sleeping, such as brushing teeth or turning off the bedroom lights. Patients with externally conditioned arousal often report that they sleep better away from their own bedroom and away from their usual routines, e.g. in a motel, on the living room couch, or in the sleep laboratory.

Laboratory tests

The effective management of insomnia requires a comprehensive evaluation of its nature including a thorough clinical interview, and different diagnostic aids (table 1) chosen according to the clinical context

Table 1

Sleep diary monitoring is of special interest in initiating and following a behavioral cognitive treatment. The various questionnaires on sleep are helpful in precising the type and severity of insomnia. Psychological tests are relevant to exclude insomnia associated with mental disorder. The Horne and Östberg questionnaire is useful when a circadian rhythm sleep disorder is suspected. Actigraphy is a simple and objective method to assess the rest-activity dimension. Polysomnography (ambulatory or in lab) allows conventional analysis of sleep continuity and architecture ; analysis of physiological features during sleep, e.g. respiration, heart rate, body temperature, etc..) ; analysis of the microstructure of sleep (spindles and K complexes, rapid eye movements, cycling alternating pattern) ; and EEG spectral analysis. Typically polysomnography reveals impairment of sleep continuity (longer sleep latency, more time awake after sleep onset, decreased sleep efficiency) and architecture (more time in stage 1 sleep, less time in stages 3-4 sleep) parameters.

Pathophysiology

A widely accepted etiological theory regarding primary insomnia attributes the condition to a special confluence of endogenous predisposing characteristics, sleep disrupting precipitating events and perpetuating behaviours or circumstances (10)

   a) Endogenous predisposing characteristics

Endogenous predisposing characteristics correspond to hyperarousal. Hyperarousal depends on physiological, cognitive and psychological factors, the respective part of each of these factors being highly variable.

- Physiological factors

Heightened autonomic arousal is characterized by faster heart rate ; more elevated frontalis muscle tension ; greater electrodermal conductance either during the presleep period, during sleep, or following nocturnal awakenings ; higher temperature both during the day and at night (11); no more tendency to sleep than normal controls on the multiple sleep latency test (12).
 Increased hypothalamic pituitary adrenal activity includes both significantly increased evening and nocturnal plasma cortisol concentration and a reduced duration of the « quiescent period » of the circadian cortisol rhythm, and a strong positive partial correlation between the evening cortisol secretion expressed as area-under-the curve

and the number of nocturnal awakenings in patients with primary insomnia (13).

Immune alterations consisting in lower levels of CD3+, CD4+ and CD8+ cells in insomnia subjects as compared with controls have been reported (14).
Excess of cyclic alternating pattern (CAP) rate is another feature of hyperarousal. During NREM sleep it is possible to identify two complementary conditions of arousal stability (NCAP) and arousal instability (CAP). Unstable sleep, which can be detected in all stages, is expressed by the recurrence of arousal complexes (K-complexes associated with spindles, alpha-like activity, delta bursts) which translate a brief (10-15sec) activation of sleeping brain (CAP), and stable sleep by the background rhythm peculiar to the sleep stage (NCPAP) (15).
Alteration of the homeostatic process of sleep is twofold. NREM sleep power, for all frequencies below the beta range, has slower rise rates and reaches lower levels in the insomniac group, whereas beta power is significantly increased. In REM sleep, insomniacs show lower levels in the delta and theta bands, whereas power in the faster frequency bands is significantly increased (16). Thus the pathophysiology of insomnia is characterized not only by the generally acknowledged slow wave deficiency, but also by an hyperarousal of the central nervous system throughout the night, affecting both NREM and REM sleep.

- Cognitive factors

They are expressed in terms of worry, racing mind, rumination, intrusive thoughts, planning, analysing, or difficulty in controlling exciting thoughts. A survey of causal attribution of insomnia among self-defined poor sleepers indicates that cognitive arousal is blamed 10 times more frequently (55%) than somatic arousal (5%) as its main determinant. Over one-third (35%) of the subjects claim that both types of arousal are important factors, while 5% endorse neither component (17)

- Psychological factors

They are reflected in elevated measures of anxiety, dysphoria, worry, somatized tension or neuroticism in general (18-20). In turn, this psychological make up may heighten the affective response of insomniacs to poor sleep (21) and trigger dysfunctional sleep cognitions. Moreover subjects with primary insomnia are more emotionally reactive to stressors and may take longer to recover from exposure to such events (22)

However there have been no prospective studies on the premorbid characteristics of persons at risk for the development of chronic insomnia. Thus most of the predisposing factors reviewed so far remain hypothetical, because they are based on retrospective and correlational evidence

b) Precipitating factors

Stress is the most common precipitating factor of insomnia. Personal losses through separation, divorce, or the death of a loved one are those most often associated with the onset of insomnia. Family-, health-, and work-related stressors naturally lead to sleepless nights. Chronic stress on the job or long-term conflicts with family members may not only trigger sleep problems but also exacerbate them.

c) Perpetuating factors

The most salient conditions maintaining insomnia consist of maladaptive sleep habits and dysfunctional cognitions about sleep loss and its impact on a person's life. Among the former are hypnotic use, excessive amounts of time spent in bed, irregular sleep schedule, napping, and among the latter, worry over sleep loss, rumination over daytime deficits, performance anxiety, fear of losing control, learned helplessness.

Narcolepsy - cataplexy

Definition

Narcolepsy-cataplexy is a chronic debilitating sleep disorder characterized by two major symptoms, excessive daytime sleepiness and cataplexy, and three so-called auxiliary symptoms, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep

Epidemiology

According to recent surveys based on both questionnaires ans polysomnography the prevalence of narcolepsy-cataplexy ranges between 0.026% (23) and 0.035% (24) in Western countries

Clinical features

Excessive daytime sleepiness occurs daily, recurring periodically at intervals that vary from patient to patient. At times excessive daytime sleepiness can be overcome, but it often builds up into irresistible sleep episodes which are of variable duration depending on the situation of the subject. Irresistible sleep episodes have a refreshing value that is of considerable diagnostic value. Excessive sleepiness can also lead to automatic behaviour. Memory problems are often reported but neuropsychological testing is generally normal.
Cataplexy is distinct from excessive sleepiness. It is pathognomonic of narcolepsy. It consists in a sudden loss of muscle tone, with preserved consciousness, triggered by emotional factors, most often positive, such as laughter, and less frequently negative, such as anger. All striated muscles may be affected, except the extraocular and respiratory musculature. Cataplectic attacks may be complete, leading to a fall. More often however, they are partial affecting facial muscles, or the neck or the upper or lower limbs. Attacks are short-lived lasting from a split second to several minutes.
The other symptoms are designed as auxiliary since they are not mandatory for the diagnosis. Hypnagogic hallucinations are mental imagery in the transition from wakefulness to sleep. Visual imagery is predominant but auditory, kinesthetic and tactile components can be encountered. The content of the hallucination is rarely pleasant. It can even be frightening. Sleep paralysis is an inability to move the limbs, the head, also in the transition from wakefulness to sleep. It is a frightening or even terrifying experience when it first occurs. In comparison with similar phenomena in normal subjects, those in narcoleptics are more frequent, of longer duration and more vivid. Nocturnal sleep is usually disrupted. Typically narcoleptics fall asleep almost instantly when they go to bed, but their sleep is afterward interrupted by repeated awakenings. Parasomnias such as nightmares and REM sleep behaviour disorders are frequent.

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Laboratory tests

Narcolepsy-cataplexy can be diagnosed on purely clinical grounds but additional tests are useful to confirm the diagnosis prior to establishing life long treatment .
On all-night polysomnography, a sleep-onset REM period (REM appearing within 20 minutes after sleep onset) is a highly specific finding. Sleep is often of poor quality with frequent awakenings, more stage 1 sleep, less stages 3 and 4, fragmentation of REM sleep, presence of dissociated sleep (25). Daytime polysomnography, e.g. the multiple sleep latency test, provides an objective measure of excessive sleepiness and demonstrates the presence of sleep-onset REM periods (SOREMPs). Sleep latencies of less than 10 minutes, characteristically below 5 minutes, and two or more SOREMPs are found in most narcoleptic patients.
HLA typing almost always shows the presence of HLA DQB1*0602 (and DR2 or DRB1*1501) in Caucasians and Asians.
Measuring CSF hypocretin-1, also called orexin A, is higly specific and sensitive to diagnose narcolepsy-cataplexy. Values below 110 pg/ml are highly specific. However up to 10% of patients with narcolepsy-cataplexy have normal CSF hypocretin-1. Thus a negative CSF test does not exclude narcolepsy-cataplexy.

Pathophysiology

Much of the knowledge in this area has been obtained from the naturally occurring animal model : canine narcolepsy (26-27). Indeed the narcoleptic dog model has a remarkable ressemblance to the human disease including cataplexy. A huge amount of neuropharmacological data has been derived using the canine model, as described in the landmark review of Nishino and Mignot (28). Excessive daytime sleepiness in narcolepsy is primarily caused by a hypoactivity of the dopaminergic system. Indeed, most stimulant medications act by increasing dopaminergic tone. Cataplexy is caused by an imbalance between pontine aminergic and cholinergic systems. Cataplexy is aggravated by cholinergic activation and/or deactivation of monoaminergic, particularly adrenergic systems. Conversely, the alpha-1 adrenergic blocker prazosine, used as an antihypertensive agent, severely worsens cataplexy.

A genetic predisposition for narcolepsy-cataplexy has been known for a long time. Starting in the 1940s, several studies investigated the familial aspect of patients' populations. Using standard diagnostic criteria, more recent studies have calculated the proportion of index cases presenting with a family history of narcolepsy-cataplexy (29-32). These studies showed a rate of 5 to 10%.
In 1984 a 100% association with the serologically determined HLA subtype DR2 was reported in Japan (33), an association later confirmed in Europe and North America. However several DR2-negative cases were later reported, suggesting the existence of other predisposing genes.
As most autoimmune disorders are linked to specific HLA haplotypes, narcolepsy-catapexy was hypothesized to be an autoimmune disease as well. However no direct evidence for an autoimmune process has been identified so far in spite of extensive studies looking for general markers of immune activation (34)
Later on high-resolution DNA-based mapping of this HLA region identified the strongest association with the subtype DQB1*0602 (35). However approximately 25% of familial cases are negative for HLA DQB1*0602 (36) supporting the existence of one or more genes with high penetrance, not associated with HLA.

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In certain breeds of dogs (Labrador retrievers, Doberman pinschers) narcolepsy-cataplexy is transmitted as an autosomal trait with complete penetrance, whereas in other breeds (Poodles, Beagles) it is polygenic and/or determined by environmental factors (37). In 1999 a positional cloning strategy led to the discovery of a mutation in the gene that codes for the hypocretin type 2 receptor, a receptor coupled to a G protein which has a high affinity for the hypocretin neuropeptides 1 and 2   (38). These neuropeptides had been identified shortly before (39).

Hypocretins 1 and 2 are produced exclusively by a well defined group of neurons localized in the lateral hypothalamus. These neurons project to the olfactory bulb, cerebral cortex, thalamus, hypothalamus and brain stem particularly to the locus coeruleus, raphe nucleus and bulbar reticular formation (40). Meanwhile endogenous ligands of two orphan receptors with homologous structures had been identified and called orexins A and B given their stimulating effects on appetite (41). These peptides turned out to be the same as those identified previously and named hypocretins. Only two weeks after the gene for canine narcolepsy was found, a second paper indicated that a null mutation, induced by a targeted modification of the orexin gene of the mouse (orexin knockout mouse) led to an autosomal recessive phenotype with characteristics reminiscent of narcolepsy-cataplexy (brief episodes of behavioral arrests and SOREMPs) (42). Based on these two studies it became clear that hypocretins (orexins) and one of their receptors, type 2 receptor, are implicated in the etiology of canine narcolepsy.

After the discovery of the mutation of the gene coding for the hypocretin-2 receptor in narcoleptic dogs, several studies were conducted in the hypocretin system in human narcolepsy-narcolepsy.

Systematic screening of mutations in hypocretin system were conducted in patients with narcolepsy-cataplexy and SOREMPs. Up to date, only one study revealed a mutation of the gene coding for hypocretin. This mutation was found in a case of atypical narcolepsy-cataplexy with an early age of onset and no association with HLA DQB1*0602 (43). On the other hand a marked reduction of hypocretin-1 was found in the CSF of narcoleptic patients suggesting a loss of peptides in the brain of narcoleptic subjects (44-45)

Genetic factors are of definite importance in narcolepsy-cataplexy. However studies in monozygotic twins suggest the importance of environmental factors in triggering the disease. Indeed of 16 pairs of identified monozygotic twins, only 4 or 5 are concordant for narcolepsy (46). A certain number of environmental factors are suspected from case reports but have never been genuinely proven to be involved in the triggering of narcolepsy-narcolepsy. Among the most commonly evoked triggers have been a severe psychological stress, an abrupt change in the sleep-wakefulness schedule, a head trauma, a viral illness (47)

Sleep disordered breathing (SDB)

Definition

SDB consists mainly in obstructive sleep apnea/hypopnea syndrome (OSAHS) which is characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway occlusion during sleep, associated with day and nighttime symptoms, and in upper airway resistance syndrome (UARS) which is characterized by sequences of breaths involving an increasing respiratory effort leading to an arousal from sleep, which

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do not meet criteria for apneas or hypopneas and which are associated with clinical manifestations very close to those of sleep apneas/hypopneas.

Prevalence

According to Young et al (48) an apnea/hypopnea index (AHI) > 15 is found in 9% of men and 4% of women, and a AHI > 5 associated with excessive daytiime sleepiness in 4% of men and 2% of women. According to Bixler et al. (49) an AHI > 10 associated with daytime symptoms is found in 3.3% of men, with a peak in the age range 45 to 64 years. An evaluation of the prevalence of UARS is not available,

Clinical features

Symptoms of OSAHS include nightime and daytime symptoms. Snoring is loud and long-standing, interrupted by respiratory pauses. Nocturnal polyuria is frequent. Other nocturnal symptoms include sudation, agitation, and fatigue and/or headache on awakening. Daytime symptoms include excessive daytime sleepiness, irritability, negligence, cognitive impairment, sexual problems in the form of reduced libido and impotence. The clinical symptoms of UARS overlap widely with those of the OSAHS, except for apneas and hypopneas

Laboratory tests

Polysomnography analyses ventilation as well as sleep continuity and architecture. During central or diaphragmatic apneas ventilatory effort is interrupted, whereas it persists during obstructive apneas. Mixed apneas begin as a central apnea and end as an obstructive apnea. UARS is defined by a pattern of progressively more negative oesophageal pressure terminated by a sudden change in pressure to a less negative level and an arousal. Sleep architecture is impaired, essentially composed of light NREM sleep. When arousals are counted irrespective of their duration, they can often number several hundreds in the course of the night. However the arousals are not usually perceived by patients, who do not habitually complain of difficulty maintaining sleep but of non restorative sleep.
The ear, nose and throat (ENT) examination focuses first on the upper oropharynx, commonly referred to as the velo-pharynx, which is where most snoring occurs, and then on the lower part of the oropharynx also referred to as the retrobasilingual pharynx, and finally, on the rhinopharyngeal and laryngeal sectors. In addition fiberoptic investigation and pharyngeal imaging, including computed tomography (CT scan) and/or cephalometric radiography are performed in the case of either prosthetic or surgical treatment orientation.

Pathophysiology of OSAHs and UARS

Upper airways behave as a Starling's resistance with a collapsible tube corresponding to the pharynx, set between two rigid segments, the nasal fossa upstream and the tracheobronchial tree downstream. According to Poiseuille's law, the flow is proportionate to the pressure difference between the extremities of the tube divided by the resistance of the system. Upstream pressure is equal to atmosphere pressure ; downstream pressure, which is variable, is generated by the activity of the inspiratory muscles ; it is best evaluated by measuring oesophageal pressure, reflecting pleural pressure. Airflow resistance depends on two factors : the negative intrathoracic pressure

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(collapse force) and the pharyngeal compliance (the capacity of the pharyngeal wall to collapse under this negative pressure), which depends on the tonicity of the pharyngeal tissues on the one hand and on the activity of the dilatory muscles on the other hand. Thus the intrathoracic pressure intervenes in two different ways in the airflow generated during inspiration : on one hand it represents the generating motor force of this flow ; on the other, it is also the force which will cause the pharynx to collapse and thus create a resistance to the passage of air.

If pharyngeal compliance is weak, the increase in respiratory pressure in response to increased resistance will not result in any change to ventilatory flow and, if the arousal threshold is high, the system will remain stable. Conversely, if the arousal threshold is low, the increase in respiratory effort will result in a micro-arousal, a sudden drop in upper airway resistance and a short increase in flow despite reduced respiratory effort. If pharyngeal compliance is high, the increase in respiratory effort will lead to enhance resistance, such that inspiratory flow is no longer maintained despite (and because of) the increase in respiratory effort. If the decrease in flow is weak, we are again in the framework of UARS ; if the decrease in flow is greater hypopnea occurs. If pharyngeal compliance is very high pharyngeal collapse will be complete, resistance is infinite, the flow is zero, and obstructive apnea occurs.

Three types of factors are involved in the occurrence of this pharyngeal collapse :
- anatomical factors : narrowing of the oropharynx or of the hypopharynx
- mechanical factors : alterations of soft tissues consecutive to the repeated microtraumatism of snoring
- neurological factors, as a failure of the command of pharyngeal muscles

In addition coexistent medical or lifestyle issues, which can be considered as environmental factors may promote upper airway dysfunction. Among these factors are obesity, sleep deprivation, variability in sleeping position, tobacco use, pharmacological agents, alcohol intake and hypothyroidism

Pathophysiology of consequences

a) Excessive daytime sleepiness

Correlational evidence suggests a relation between sleep fragmentation and daytime sleepiness.
Fragmentation, as indexed by the number of brief EEG arousals, number of shifts from other sleep stages to stage 1 sleep or wakefulness, and the percentage of stage 1 sleep, correlates with excessive daytime sleepiness in various patient groups (50). Patients with OSAHS, who are significantly treated by surgery (reduction of the number of apneas/hypopneas) show a reduced frequency of arousals from sleep as well as reduced levels of sleepiness, whereas those who do not benefit from the surgery (apneas remain) show no decrease in arousals or sleepiness, despite improved sleeping oxygenation (51). Similarly, continuous positive airway pressure (CPAP) by providing a pneumatic airway splint, reduces breathing-disturbances and consequent arousals from sleep, and reverse excessive daytime sleepiness (52)

b) Hypertension

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Each of the partial or complete interruptions of airflow characterizing the OSAHS fragments sleep and involves a substantial transient post-apneic rise in blood pressure (53). Moreover the repetition of respiratory events over a period of several weeks in a canine model is able to induce permanent hypertension (54).

Several epidemiologic studies have confirmed a role of apneas/hypopneas in the development of hypertension in humans. The US National Sleep Heart Study has established a relative risk between 1,37 and 2.27 for an apnea/hypopnea index greater than 30/h (55). Of even more interest are the results of the analysis of data on sleep-disordered breathing, blood pressure, habitus, and health history at baseline and after four years of follow-up, in 709 participants of the Wisconsin Sleep Cohort Study (and after eight years of follow-up in the case of 184 of these participants) revealing a risk of 1.42 for an apnea/hypopnea index between 5 and 15 and a risk of 2.89 for an apnea/hypopnea index between 5 and 15, after adjustment for baseline hypertension status, body-mass index, neck and waist circumference, age, sex, and weekly use of alcohol and cigarettes (56). Whether or not OSAHS constitutes an independent risk factor is a debated issue. According to the Oxford group, an independent risk factor between OSAHS and diurnal blood pressure does exist. However its amplitude and clinical significance have still to be established (57).

c) Coronary heart disease

An association between OSAHS and coronary heart disease has been suggested by several studies (58-60). These studies, however, were criticized because they did not properly adjust for all important confounding factors. According to the Wisconsin study (n=1206) the prevalence of coronary heart disease increases with the AHI (61). After adjusting for sex, age and body mass index the relative risk is 1.2 for an AHI of 2 to 15, 1.5 for an AHI of 15 to 30 and 3 for an AHI > 30. In the Sleep and Heart Heath Study (n=6424), the relative risk of hypertension increases with AHI, but the relative risk of coronary heart disease, which appears for rather modest AHI (1.28 for an AHI of 5 to 11 ; 1.42 for an AHI > 11), remains stable beyond this limit after adjusting for age, ethnic group, sex, tobacco, arterial hypertension, diabetes mellitus and total cholesterol (62). However in a case-control study matching for age, sex and body mass index (BMI), and additionally adjusting for hypertension, hypercholesterolemia, diabetes mellitus and current smoking, a univariate logistic regression analysis showed that current smoking, diabetes mellitus, and OSAHS, but not hypertension and hypercholesterolaemia were significantly correlated with coronary artery disease, and in the same study, using a multiple logistic regression model, current smoking, diabetes mellitus and OSAHS all remained independently associated with coronary artery disease (63).

d) Stroke

A close relationship between sleep-disordered breathing (SDB) and stroke has been recognised, and data are accumulating supporting the hypothesis that SDB may play an important role in the pathophysiology of stroke and its evolution. A large cross-sectional study (62) confirmed the association of SDB, not only with coronary heart disease but also with stroke. Several publications suggest that SDB may increase stroke through various mechanisms including blood pressure swings, endothelial dysfunctions, prothrombotic coagulation shifts, pro-inflammatory state, increased platelet aggregation and atherosclerosis.

However it is not yet clear whether patients with polysomnographically proven SDB have an elevated cerebrovascular morbidity that is independent of the associated vascular risk profile (64)

e) Cognitive impairment

Numerous studies have assessed a wide range of cognitive deficits associated with OSAHS. Although these studies have used different neurophysiological tests and different patient populations, various degrees of impairment of selective attention (concentration), sustained attention (vigilance), short and long term memory, and executive functions, have been evidenced (65) . It is very likely that both sleep fragmentation and hypoxemia play a role in these deficits. However it is still difficult to determine the respective contributions of these two factors

Environmental sleep disorder

Definition

Environmental sleep disorder is a sleep disturbance due to a disturbing environmental factor that causes a complaint of either insomnia or excessive sleepiness.

Prevalence

Although the prevalence of environmental sleep disorder is not known, transient sleep disturbances of this nature are likely to be very common. The percentage of the general population with chronic environment-induced sleep disorders has not been determined.

Clinical features

Environmental sleep disorder caused by sleeping in unfamiliar surroundings tends to affect subjects who are used to strict bedtime routines.
Among the measurable physical factors likely to lead to insomnia, noise has undoubtedly been the most frequent subject of study. With weak noise stimulation minimal alterations can be detected in polygraphic recording, such as the appearance of isolated K complexes, short bursts of alpha waves or the momentary disappearance of delta waves. At one stage higher « transient activation phases » are seen in sleep with the return of alpha rhythms for periods of several seconds, which are insufficient to score the epoch as wakefulness (66-67). At a still higher level, noise alters sleep with the introduction of increased movements, arousals and changes in sleep stages (68-69). The amount of time awake and in stage 1 increases, while the amount of NREM sleep and REM sleep may be reduced. Sensitivity to noise varies widely from one individual to another, in terms of intensity as well as significance. Some mothers will wake at the slightest whimper from their child yet sleep throug a storm.
Inadequate temperature, e.g. too low or too high, is also likely to disturb sleep. The amount of time awake and in stage 1 increases while the amont of REM sleep diminishes (70). The cold is more harmful to sleep than is the heat.

Laboratory tests

Diagnosis of environmental sleep disorder does not rely on laboratory tests, but on interviewing the subject

Pathophysiology

Environmental sleep disorder is a sleep disturbance due to a disturbing environmental factor that causes a complaint of either insomnia or excessive daytime sleepiness. Residence near a busy airport or highway, a sleeping environment that is poorly heated in cold seasons of the year or inadequately air conditioned in warm months, a bedpartner who snores or is restless, and responsibility for a newborn infant or an invalid are all predisposing factors for environmental sleep disorder with insomnia. Routine and monotonous vocations, social isolation, and physical confinement are predisposing factors for environmental sleep disorder with excessive sleepiness. Hospitalization that results in imposed abnormal sleep-wake schedules or discomfort may contribute to environmental sleep disorder. However the sensitivity of the patient to such environmental sleep disturbances is often more critical than the level of noxious stimulation.

Periodic limb movement disorder (PLMD)

Definition

PLMD consists in periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep. It is most often preceded by restless legs syndrome (RLS) which occurs during wakefulness, particularly at bedtime, and is characterized by an irresistible urge to move the legs, associated with paresthesias, at least partially relieved by movement especially by walking

Prevalence

The prevalence of PLMD increases substantially with age. It is estimated that 5% of normal subjects in between 30 and 50 years of age have a pathological index of PLMs with polysomnography, while this percentage may increase to almost 30% in subjects of over 50 years of age and 44% for those over 65 years (71)

Clinical features

Periodic leg movements (PLMs) take the form of periodic extension of the big toe and dorsiflexion of the foot, occasionally with flexion of the knee and hip. Movements usually last a few seconds, occur periodically, roughly every 30 seconds, and are more numerous during the first half of the night.

Laboratory tests

These movements are characterized by a sustained contraction or a polyphasic burst. A movement index of more than 5 per hour of sleep is considered pathological. They are often associated with arousals, although some patients present a large number of PLMs with no arousals or substantial modification of the general architecture of sleep. PLMD

patients may complain of frequent nocturnal awakenings, unrefreshing sleep or excessive daytime sleepiness.

The phenomenon may appear in normal subjects, but it is often associated with a wide variety of sleep disorders such as insomnia, narcolepsy, OSAHS.

Pathophysiology

From a neurophysiological point of view the periodic nature of nocturnal leg movements suggests the presence of a rhythmic generator in the central nervous system. Studies carried out on cats and humans, either asleep or in a coma, have helped to reveal the regular variations in blood pressure, heart beat, respiration rate, intraventricular pressure and EEG during the course of sleep. The mean variation period is comparable to that of the PLMs, varying from 20 to 60 seconds. Moreover, in RLS patients with PLMs, periodic arousals persist during the night after the suppression of movements by pharmacological treatment (72). These results suggest that the periodic arousals may not be secondary to movements but, on the contrary, directly involved in the mechanisms responsible for their occurrence.

From a neurochemical point of view, there is substantial evidence to suggest that dopamine is implicated in the pathophysiology of RLS and PLMs. First of all, L-dopa, which predominantly increases concentrations of dopamine, and bromocriptine, a D-2 receptor agonist, inhibit both RLS and PLMs (73). Furthermore, PLMs are worsened by administering pimozide, a D2 receptor antagonist (74). In addition a recent study using PET functional imagery showed that in 13 patients presenting RLS, the link to D2 receptors was significantly reduced in the striatum (75). These results suggest that RLS and PLMs are caused by a reduced dopamine transmission.

Conclusion

In the framework of this conference it is certainly relevant to raise the question of whether or not any of these disorders may serve as a model or at least may shed some light on the issue of sleep disorders caused by noise

Concerning primary insomnia it has been shown that the pathophysiology of the disorder is considered to be based on the confluence of predisposing, precipitating and perpetuating factors. Along this line, in a predisposed subject, noise may certainly act as a triggering factor.

Narcolepsy-cataplexy is most often remarkable for sleep fragmentation. However, in contrast to the obstructive apnea/hypopnea syndrome there is no correlation between sleep fragmentation and excessive daytime sleepiness (76). Moreover the pathophysiology of narcolepsy is based on an imbalance between acetylcholine and monomaines and on an impairment of the hypocretin system, which are not found in noise induced insomnia

A polysomnographic feature of OSAHS and UARS, consists in recurrent arousals and awakenings. Interestingly, most of subjects with these conditions do not complain of poor sleep, but of non-restorative sleep, fatigue and/or headache on morning awakening, and excessive daytime sleepiness. These clinical features are certainly an incentive to look for morning symptoms and excessive daytime sleepiness in subjects submitted to an abnormal level of noise.

Environmental sleep disorder has noise as one of its possible sources, may be the most important one. Two issues have been emphasized. First, environmental disorder does

not refer only to insomnia but also to excessive sleepiness, so that the possiblity of excessive daytime sleepiness in subjects undergoing a noisy environment must be kept in mind. Second, vulnerability to either insomnia or hypersomnia, must be considered in subjects at risk for environmental sleep disorder.

Finally arousals and awakenings are a polysomnographic feature of periodc limb movement disorder. However PLMs do not seem to be the cause of arousals and awakenings. On the other hand PLMs and arousals / awakenings may depend on a common mechanism.

References

1) American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th edition). American Psychiatric Association, Washington, DC. 1994
2) Morin CM. Sleep impairment index. In : Insomnia : Psychological assessment and management. 1993 :199-200
3) Morin CM. Beliefs and attitudes about sleep scale. In : Insomnia : Psychological assessment and management. 1993 : 201-204
4) Buysse DJ, Reynolds III C.F, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index : a new instrument for psychiatric practice and research. Psychiatry Research 1989 ; 28 : 193-213
5) Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in Psychopharmacological Investigations – a review. Psychopharmacology 1980, 2, 173-179.
6) Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for Measuring Depression. Arch gen Psychiatry 1961 ; 4 : 561-571
7) Spielberger CD, Gorsuch RL, Lushene R et al. The State-Trait Anxiety Inventory for Adults. Palo-Alto, California : mind Garden. 1983
8) The Mini-International Neuropsychiatric Interview (M.I.N.I.) : the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998 ; 59 Suppl. 20 :22-33
9) Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976 ; 4 : 97-110
10) Spielman AJ. Assessment of insomnia. Clinical Psychology Review. 1986 ; 6 : 11-26
11) Monroe LJ. Psychological and physiological differences between good and poor sleepers. Journal of Abnormal Psychology. 1967 ; 72 : 255-264
12) Stepanski E, Zorich F, Roehrs TA, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. Sleep 1988 ; 11 : 54-60
13) Rodenbeck A, Hajak G. Neuroendocrine dysregulation in primary insomnia. Rev Neurol (Paris) 2001 ; 157 : 5S57-5S61.
14) Savard J, Laroche L, Simard S, Ivers H, Morin CM. Chronic insomnia and immune functioning. Psychosom Med 2003 ; 65 : 211-221
15) Terzano MG, Parrino L. Clinical applicatios of the cycling alternating pattern (CAP). Sleep Medicine Reviews, 2000 ; 4 : 101-123.
16) Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. Eur J Neuroscience 1998 ; 10 : 1826-1834.
17) Lichstein KL , Rosenthal TL. Insomniacs' perceptions of cognitive versus somatic determinants of sleep disturbance. J of Abn Psychol 1980 ; 89 : 105-107.
18) Freedman RR, Sattler HL. Physiological nd psychological factors in sleep-onset insomnia. J of abn Psychol 1982 ; 91 : 380-389
19) Hauri PJ, Fisher J. Persistent psychophysiological (learned) insomnia. Sleep, 1986 ; 9 : 38-53.
20) Edinger J, Stout AL, Hoelscher TJ. Cluster analysis of insomniacs' MMPI profiles. Relationof subtypes to sleep history and treatment outcome. Psychosoamtic Med 1988 ; 50 : 77-87.
21) Coyle K, Watts FN. The factorial structure of sleep dissatisfaction. Behaviour Research and Therapy 1991 ; 29 : 513-520
22) Waters WF, Adams S, Binks P, Varnado P. Attention, stress, and negative emotion in persistent sleep-onset and sleep-maintenance insomnia. Sleep 1993 ; 16 : 128-136
23) Hublin C, Kaprio J, Partinen M, Koskenvuo M, Heikkilä K, Kosmikies S et al. The prevalence of narcolepsy : an epidemiological study of the Finnish twin cohort. Ann Neurol 1994 ; 35 : 709-716
24) Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota : a population-based study. Sleep 2002 ; 25 : 197-202

25) Montplaisir J, Billiard M, Takahashi S, Bell IR, Guilleminault C, Dement WC. Twenty-four-hour recording in REM narcoleptics with special reference to nocturnal sleep disruption. Biol Psychiatry 1978 ; 13 : 73-89

26) Knecht C, Oliver J, Redding R, Selcer R, Johnson G. Narcolepsy in a dog and a cat. J Am Vet med Assoc 1973 ; 162 : 1052-1053

27) Mitler MM, Boysen BG, Campbell L, Dement WC. Narcolepsy cataplexy in a female dog. Exp Neurol 1975 ; 45 : 332-340

28) Nishino S, Mignot E. Pharmacological aspects of jhuman and canine narcolepsy. Prog Neurobiol 1997 ; 52 : 27-78

29) Honda Y. Clinical features of narcolepsy : Japanese experiences. In : Y. Honda, T. juji (eds) HLA in narcolepsy. Springer-Verlag, Berlin, 1988 : 24-57

30) Guilleminault C, Mignot E, Grumet FC. Familial patterns of narcolepsy. Lancet 1989 ; 335 : 1376-1379

31) Billiard M, Paquié-Magnetto V, Heckmann M, Carlander B, Besset A, Zachariev Z et al. Family studies in narcolepsy. Sleep 1994 ; 17 : S54-S59

32) Nevsimalova S, Mignot E, Sonka K, Arrigoni JL. Familial aspects of narcolepsy-cataplexy in the Czech Republic. Sleep 1997 ; 20 :1021-1026

33) Juji T, satake M, Honda Y, Doi Y. HLA antigens in Japanese patients with narcolepsy. Tissue Antigens 1984 ; 24 : 316-319.

34) Lin L, Hungs M, Mignot E. Narcolepsy and the HLA region. J. Neuroimmunol. 2001 ; 117 : 9-20

35) Mignot E., Lin X, Arrigoni J, Macaubas C, Olive F, Hallmayer J et al. DQB1*0602 and DQA1*0102 (DQ1) are better marker than DR2 for narcolepsy in Caucasian and Black Americans. Sleep 1994 ; 17 : S60-S67.

36) Mignot E, Meeyan J, Grumet FC, Hallmeyer J, Guilleminault C, Hesla PE. HLA class II and narcolepsy in thirty-three multiplex families. Sleep res 1996 ; 25 : 303

37) Foutz AS, Mitler MM, Cavali-Sforza LL, Dement WC. Genetic factors in canine narcolepsy. Sleep 1979 ; 1 : 413-422

38) Lin L, Faraco J, li R, Kadotani H, Rogers W, Lin X et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene ? Cell 1999 ; 98 : 365-376

39) De Lecea L, kilduff TS, Peyron C, Gao XB, Foye PE, Danielson PE et al. The hypocretins : hypothalamic specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1998 ; 95 : 322-327

40) Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al ; Neurons containing hypocretin (orexin) project to multiple neuronal system. J neurosci 1998 ; 18 : 9996- 10015

41) Sakurai T, Amemiya A, Ishii M, Matsukazi I, Chemelli RM, Tanaka H et al. Orexin and orexin receptors : a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behaviour. Cell 1998 ; 92 : 573-585

42) Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammel T, Lee C et al. Narcolepsy in orexin knockout mice : molecular genetics of sleep regulation. Cell 1999 ; 98 : 437-451.

43) Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y et al ; A mutation in a case of erly onset narcolepsy and a generalized absence of hypocretin petides in human narcoleptic brains. Nat Med 2000 ; 6 : 991-997

44) Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy . lancet 2000 ; 355 : 39-40

45) Nishino S, Ripley B, Overeem S, Nevsimalova S, Lammers GJ, Vankova J, et al ; Low CSF hypocretin (orexin) and altered energy homeostasis in human narcolepsy. Ann Neurology 2001 ; 50 : 381-388.

46) Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998 ; 50 : S16-S22

47) Orellana C, Villemin E, Tafti M, Carlander B, Besset A, Billiard M. Life events in the year preceding the onset of narcolepsy. Sleep 1994 ; 17 : S50-S53.

48) Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993 ; 328 : 1230-1235

49) Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men : l. Prevalence and severity. Am J Respir Crit Care Med 1998 ; 157 : 144-148.

50) Stepanski E, Lamphere J, Badia P, Zorick F, Roth T. Sleep fragmentation and daytime sleepiness. Sleep 1984 ; 7 : 18-26

51) Zorick F, Roehrs T, Conway W, Fujita S, Wittig R, Roth T. Effects of uvulopalatopharyngoplasty on the daytime sleepiness associated with sleep apnea syndrome. Bull Eur Physiopathol Respir 1983 ; 19 : 600-603

52) Lamphere J, Roehrs T, Wittig R, Zorick F, Conway WA, Roth T. Recovery of alertness after CPAP in apnea. Chest 1989 ; 96 : 1364-1367.

53) Davies RJO, Belt PJ, Robert SJ, Ali NJ, Stradling JR. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. J Appl Physiol 1993 ; 74 : 1123-1130.

54) Brooks D, Horner RL, Kozar LF, Render-Teixera CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997 ; 99 : 106-109

55) Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA 2000 ; 283 : 1829-1836

56) Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep disordered breathing and hypertension. N Engl J Med 2000 ; 342 : 1378-1384

57) Pepperell JCT, Davies RJO, Stradling JR. Systemic hypertension and obstructive sleep apnoea. Sleep Med Rev 2002 ; 6 : 157-173

58) Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet 1990 ; 336 : 261-264

59) Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in women : occurrence and association with coronary artery disease. Am J Med 1990 ; 101 : 251-256

60) Mooe T, Rabben T, Wilklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. Chest, 109 : 659-663

61) Young T, Peppard P. Sleep-disordered breathing and cardiovascular disease epidemiologic evidence for a relationship. Sleep 2000 ; 23 (suppl 4) : 122-126

62) Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto J. et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001 ; 163 : 19-25

63) Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. Eur Respir J 1999 ; 14 : 179-184

64) Hermann DM, Bassetti CL. Sleep-disordered breathing and stroke. Curr Opinion in Neurology 2003 ; 16 : 87-90

65) Décary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome : a proposed neuropsychological test battery. Sleep, 2000 ; 23 : 369-381

66) Ehrart J, Muzet A. Fréquence et durée des phases d'activation transitoire au cours du sommeil normal ou perturbé chez l'homme. Arch Sci Physiol 1964 ; 28 : 213-260

67) Schieber JP, Muzet A, Ferrière PJ. Le phases d'activation transitoire spontanées au cours du sommeil normal chez l'homme. Arch Sci Physiol 1971 ; 25 : 443-465

68) Vallet M, Mouret J. Sleep disturbance due to transportation noise= : ear plugs or oral drugs. Experientia 1984 ; 40 : 429-437

69) Muzet A. Les effets du bruit sur le sommeil. C R Soc Biol 1989 ; 183 : 437-422

70) Gallup Organization. Sleep in America. Princeton NJ, The Gallup Organization, 1991

71) Montplaisir J, Nicolas A, Lapierre O. Restless legs syndrome in wakefulness and periodic leg movements in sleep. In M. Billiard (ed) Sleep : Physiology, Investigations and Medicine. Kluwer Academic/Plenum Publishers, New York, NY, 2003 : 599-607

72) Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-Dopa. Sleep 1996 ; 19 : 196-199

73) Montplaisir J, Godbout R, Poirier G, Bédard MA. Restless legs syndrome and periodic movements in sleep : physiopathology and treatment with L-dopa. Clinical Neuropharmacology, 1986 ; 9 : 456-463.

74) Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. Clinical Neuropharmacology, 1987 ; 10 : 69-79

79

75) Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome : 18F-dopa and 11C-raclopride PET studies. Neurology, 1999 ; 25 : 932-937.

76) Broughton R, Dunham W, Weisskopf M, Rivers M. Night sleep does not predict day sleep in narcolepsy. Electroencephalogr Clin Neurophysiol 1994 ; 91 : 67-70

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Table I

Diagnostic aids for the investigation of chronic insomnia

Sleep diary monitoring

Sleep questionnaires

- Sleep impairment index (2)
- Beliefs and attitudes about sleep scale (3)
- Pittsburg sleep quality index (4)
- Leeds sleep evaluation questionnaire (5)

Psychological tests

- The Beck Depression Inventory (6)
- The Spielberger State-Trait Anxiety Scale (7)
- The Mini International Neuropsychiaric Interview (M.I.N.I.) (8)

Questionnaire used in the evaluation of circadian rhythm sleep disorder

- The Horne and Östberg Questionnaire (9)

Actigraphy

Polysomnography

Sleep disorders in children, mechanisms through which sleep disorders affect the health of children – A. Wiater

A. Wiater*, G. Lehmkuhl**, S. Kraenz**, A. Mitschke*,
L. Fricke**, U. Breuer**
*Department for Pediatrics, Hospital Cologne-Porz, Cologne, Germany
**Department for Psychiatry and Psychotherapy of the Child,
University of Cologne, Germany

1. Summary

Main sleep disorders in children include intrinsic and extrinsic sleep disorders as well as parasomnias. Intrinsic sleep disorders comprise disorders like the obstructive sleep apnea syndrome that can affect the health of children in the form of somatic disorders, e.g. cardiovascular or respiratory problems. Predominantly, extrinsic sleep disorders occur during childhood. Inadequate sleep hygiene, environmental sleep disorder, adjustment sleep disorder, limit-setting sleep disorder, and sleep-onset association disorder belong to this category. Extrinsic sleep disorders are strongly associated with behavior problems like hyperactivity or psychological symptoms. Parasomnias, especially nightmares, can also be associated with psychological problems. Due to sleep disorders, many children are unrefreshed in the morning and present with daytime sleepiness. Up to 35% of elementary school children present with sleep onset problems and 21% of this group have problems to sleep through the night. Usually, several sleep disorders can be diagnoesed in one child. Educational efforts to make the children used to regular bedtimes and wake times from early on could be helpful for a normal sleep-wake-rhythm. Environmental factors, like noise disturbances, can influence children's sleep. 15% of elementary school children complain about noise disturbances during sleep. The main source of noise is the road traffic noise. Noise disturbances are one cause of sleep disorder-dependent health risks. Too little is known about the connection between noise disturbances during children's sleep and their sequelae. Direct effects of noise-induced sleep disturbances on health must be considered as well as later developmental problems that may occur during adulthood. Therefore, further studies are necessary in order to establish specific prevention programs for children.

2. Introduction

Sleep disorders in children are classified according to several classifications. The most subtly differentiated classification is the **International Classification of Sleep Disorders (ICSD)**. This classification was produced primarily for diagnostic and epidemiological purposes in pediatric and adult sleep medicine. The ICSD consists of 84 disorders, round about half of them can be applied to infants and children. Diagnostic criteria have been developed to aid in the diagnosis of a particular disorder. Insofar, criteria like sleepiness and insomnia are clearly defined. The ICSD is consistent in style with International Classification of Diseases (ICD) classifications for disorders affecting systems such as the cardiovascular or respiratory. The ICSD is not compatible with the Diagnostic and Statistical Manual III-R that contains an abbreviated list of sleep disorders.

Mechanisms through which sleep disorders affect the health of children have been evaluated in several studies, recently in a German study including 11500 school children. Up to 35% of the elementary school children present with sleep onset delays, 21% of this group have problems to sleep through the night. There are strongly increased risks for behavior problems among children with sleep onset problems, problems to sleep through the night and daytime sleepiness. On the other hand, severe forms of sleep-related breathing disorders in infants and children may be associated with cor pulmonale, developmental delay, failure-to-thrive, or death.

Environmental factors that influence children's sleep are light and noise disturbances during the night as well as television-viewing and playing video games before sleep. 15% of the 9-11 years-old children complain about noise disturbances during the night.

Sleep disorders in children are widespread complex disorders in direct connection with the daytime behavior. The development and evaluation of disorder-specific prevention and treatment concepts is urgently needed.

3. Main sleep disorders in children

The ICSD comprises four categories:

Dyssomias, i.e. disorders of initiating and maintaining sleep and the disorders of excessive sleepiness. Dyssomnias are divided into three groups: Intrinsic, extrinsic and circadian-rhythm sleep disorders. One well-known example for an intrinsic dyssomnia in children and adults is the obstructive sleep apnea syndrome. There are difficulties in maintaining sleep because of awakenings following oxygen desaturations. As a result of the sleep disruption patients develop an excessive daytime sleepiness, so that both criteria of dyssomnia coincide in this disorder.

Parasomnias comprise the disorders of arousal, partial arousal, or sleep stage transition, which do not cause a primary complaint of insomnia or excessive sleepiness. Parasomnias
intrude into the sleep process and are not primarily disorders of sleep and wake states per se. Parasomnias are divided into four groups: arousal disorders, sleep-wake transition disorders, parasomnias usually associated with rapid eye movement (REM) sleep, and other parasomnias. One example is sleepwalking. After returning to bed the sleepwalker continues to sleep without reaching alertness at any point and he or she is amnestic for the episode's events.

Sleep disorders associated with mental, neurologic, or other medical disorders comprise disorders with a prominent sleep complaint that is felt to be secondary to another condition. The listing of mental, neurologic, or other medical disorders does not include all mental and medical disorders that affect sleep and wakefulness, however those, most commonly associated with sleep symptoms. Examples are psychoses, sleep-related epilepsy and sleep related asthma or gastroesophageal reflux.

Proposed sleep disorders include those disorders for which there is insufficient information available to confirm their acceptance as definitive sleep disorders. Some sleep disorders that are controversial as to whether they are extremes of the normal range or represent a definitive disorder of sleep are included here, i.e., short sleeper and long sleeper.

In the following, according to the ICSD, sleep disorders in children are listed:

Dyssomnias

A. Intrinsic sleep disorders

Most important in pediatrics of this group is the **obstructive sleep apnea syndrome**. Up to 3% of the pre-school children are affected. The obstructive sleep apnea syndrome is characterized by repetitive upper airway obstructions during sleep, usually associated with blood oxygen desaturations. Children can exhibit loud habitual snoring, arousals, and unusual sleep positions, such as sleeping on hands and knees. Some children present with noisy breathing, some with quiet obstructions. Nocturnal enuresis is common. Because of the sleep disturbance, the children are unrefreshed in the morning and may develop excessive daytime sleepiness or hyperactivity. The obstructive sleep apnea syndrome of children is often caused by an adenotonsillar hypertrophy. Untreated it may be associated with cor pulmonale, developmental delay, failure-to-thrive, or death. After the operative removal of adenoids and tonsils most of the children are cured. Sometimes nCPAP-therapy during sleep is mandatory.

OBSTRUCTIVE SLEEP APNEA SYDROME
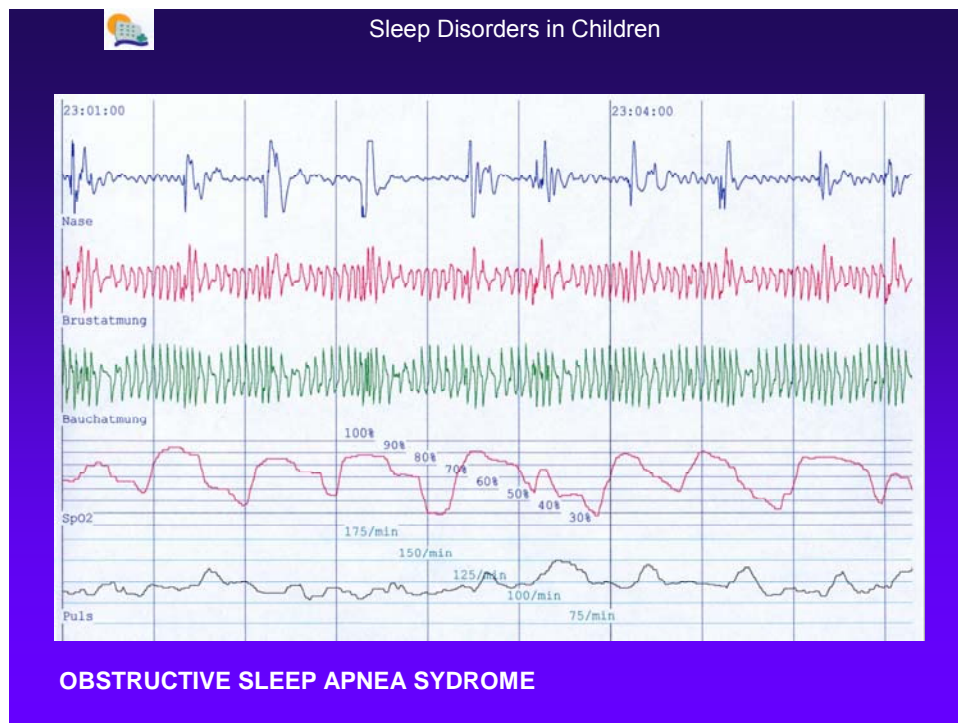
The **central sleep apnea syndrome** is characterized by a cessation or decrease of ventilatory effort, usually associated with blood oxygen desaturations. Children are seldom affected.

The **central alveolar hypoventilation syndrome** is characterized by ventilatory impairment, resulting in sleep-related blood oxygen desaturations, occurring in patients with normal mechanical lung function. The syndrome is known as obesity hypoventilation syndrome. In nonobese patients, the syndrome can be considered to be idiopathic, and

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a primary disorder of respiratory control can be inferred. Central nervous system depressants may precipitate central alveolar hypoventilation during sleep. Neurologic lesions, such as infection, infarction may lead to the acquired form of the disorder. Both forms of the disorder, the idiopathic form as well as the acquired form can occur during childhood.

Narcolepsy is characterized by excessive sleepiness that typically is associated with cataplexy, sleep paralyses and hypnagogic hallucinations. 20-30/million children under 18 years are affected. The peak incidence is around 14 years of age. Excessive sleepiness is usually the first symptom to appear. Cataplexy appears either simultaneously or with a delay of 1 or more years. It rarely precedes the onset of sleepiness. Because of the unspecific beginning of the disorder, the diagnosis setting is often delayed.

B. Extrinsic Sleep Disorders

Extrinsic sleep disorders include disorders that originate or develop from outside. External factors produce these disorders, and the removal of these factors leads to resolution of the sleep disorder. This is not to say that internal factors can be important in the development or maintenance of the sleep disorder, just as external factors can be important in the development and maintenance of an intrinsic sleep disorder. However, the internal factors by themselves would not have produced the sleep disorder without presence of an external factor. On the other hand, the diagnosis of an extrinsic sleep disorder is only made when the external factors, i.e. environmental factors like excessive noise or extreme lighting effects are particularly abnormal and would produce sleep disturbance in most people. Extrinsic sleep disorders are the predominant sleep disorders during childhood.

Inadequate sleep hygiene is a sleep disorder due to practices of daily living that are inconsistent with the maintenance of good-quality sleep and full daytime alertness. Especially, there are practices that produce increased arousal and practices that disturb sleep organization. Stress and excitement, such as to much exercise close to bedtime, playing at night, uncomfortable ambient temperature are factors causing increased arousals. Sleep may become disrupted when there is excessive daily variation in bedtime, arising time, and amount of sleep.

Environmental sleep disorder is due to a disturbing environmental factor that causes a complaint of either insomnia or excessive sleepiness. The sleep complaint is tied directly to a causative environmental condition. Sleep-disturbing circumstances include heat, cold, noise, light and others. The sensitivity of the patient to such environmental circumstances is often more critical than the level of noxious stimulation. Sensitivity to environmental disturbances in nocturnal sleepers increases towards morning. Older individuals are generally more sensitive to environmental factors than are younger ones, although substantial variability in sensitivity may be noted in a particular age group. Three conditions must be present to make a diagnosis of environmental sleep disorder: (1) the sleep problem is temporally associated with the introduction of a physically measurable stimulus or definable set of environmental circumstances, (2) the physical rather than the psychologic properties of the environmental factors are the critical causative elements, and (3) removal of the responsible factors results in an immediate or gradual return to normal sleep and wakefulness.
Mental status examination and psychologic evaluation reveal no psychiatric explanation of sleep complaint. Physical examination reveals no underlying medical cause.

Depending on the chronicity and the extent of sleep disturbance resulting from the environmental cause, secondary symptoms, including deficits in concentration, attention, and cognitive performance, reduced vigilance, daytime fatigue, depressed mood, and irritability may result. In childhood, noise-induced, light-induced, and temperature-induced sleep disturbances mainly cause environmental sleep disorders.

Adjustment sleep disorder represents sleep disturbance temporally related to acute stress, conflict, or environmental change that causes emotional arousal. Adjustment sleep disorder may occur at any age. Children with this disorder apparently are more likely to present with insomnia than daytime sleepiness. Examples are insomnia in the week preceding the first day of school, or in reaction to school- or family-related problems.

Limit-setting sleep disorder is primarily a childhood disorder that is characterized by the inadequate enforcement of bedtimes by a caretaker, with the patient then stalling or refusing to go to bed at an appropriate time. It also occurs after nighttime wakings. Limit-setting sleep disorder is both, a childhood disorder and a caretaker complaint. If appropriate limits cannot be set, it can become a problem of poor sleep hygiene, irregular scheduling, and insufficient sleep in adulthood.
Setting limits can become a problem if parents give in to requests made by a child in the bed. Requests are typically for an extra drink, to make a trip to the bathroom, to be tucked in again, to have a light turned on or off, to have another story, to watch television, or to have help dealing with fear. Often when a certain level of exacerbation is reached, caretakers do enforce limits, and the child stays in bed and goes to sleep.

Sleep-onset association disorder occurs when sleep onset is impaired by the absence of a certain object or set of circumstances. It is mainly a disorder of childhood. Sleep is normal when certain conditions are present; when they are not, transitions to sleep, both at bedtime and after nighttime wakings, are delayed. Conditions associated with sleep onset are e.g., rocking, sucking a pacifier, replacing the pillow, pulling up the blanket, and story reading. Often symptoms of sleep-onset association disorder persist until age three or four. Occasionally, bedtime rituals change and symptoms may persist longer.

Food allergy insomnia is a disorder of initiating and maintaining sleep due to an allergic response to food allergens. The sleep disturbance is typically one of difficulty initiating sleep and of frequent arousals and awakenings. Additional symptoms include crying, psychomotor agitation and daytime symptoms. Other symptoms of allergy may accompany the sleep disturbance e.g., skin irritation, respiratory difficulties, or gastrointestinal upset. Food allergy insomnia usually begins in infancy and can resolve by age two to four years. Often a specific treatment is necessary.

Nocturnal eating (drinking) syndrome is characterized by recurrent awakenings, with the inability to return to sleep without eating or drinking. The condition is primarily a problem of infancy and early childhood, with intake of large volumes by nursing or bottle-feeding at times of waking. After the patient consumes the expected amount of food or liquid, return to sleep is rapid. Infants are usually nursed to sleep and then again repeatedly during the night. The association of nursing with sleep onset is thus important, but the large number of wakings (typically three to eight) is usually greater than is seen when only the learned sleep-onset associations represent the problem. True hunger signals are presumed to be present by the way the child takes the feeding, but the timing of these hunger symptoms seems to be learned rather than representative

of a true nutrition requirement. Full-term, normally growing, healthy infants of six months of age or more should have the ability to sleep through the night without requiring feedings.

C. Circadian-Rhythm Sleep Disorders share a common underlying chronophysiologic basis. The major feature is a misalignment between the patient's sleep pattern and the sleep pattern that is desired or regarded as the societal norm. Concerning the **delayed sleep-phase syndrome**, adolescence appears to be the most common period of life for the onset of this disorder, but childhood cases have been reported. **Non-24-hour sleep-wake disorder** has been described in congenitally blind infants.

Parasomnias
A. Arousal Disorders
The disorders of arousal are grouped together because impaired arousal from sleep has been postulated as a cause for these disorders. The onset of these disorders in slow-wave sleep is a typical feature. Confusional arousals most commonly occur in children and have features in common with both sleepwalking and sleep terrors. They are probably partial manifestations of sleepwalking and sleep-terror episodes. They can occur in people who have either or both disorders. Or confusional arousals may occur as an isolated sleep disorder. The diagnosis of confusional arousal is only stated if the arousal occurs as an isolated sleep disorder.

Confusional arousals consist of confusion during and following arousals from sleep, usually from deep sleep in the first part of the night. The individual is disoriented in time and space, is slow of speech and mentation, and responds poorly and slowly to command or questioning. There is major memory impairment, both retrograde and anterograde in type. Behavior may be very inappropriate. The Confusional behavior may last from several minutes to several hours. Confusional arousals can be precipitated by forced awakenings, mainly in the first third of the night.

Sleepwalking consists of a series of complex behaviors that are initiated during slow-wave sleep and result in walking during sleep. The patient may be difficult to awaken but, when awakened, often is mentally confused. The patient is usually amnestic for the episode's events. Sleepwalking originates from slow-wave sleep and, therefore, is most often evident during the first third of the night or during other times of increased slow-wave sleep, such as after sleep deprivation. The motor activity may terminate spontaneously. Sleep talking can also be observed during these events. Sleepwalking can include inappropriate behavior, it can furthermore result in falls and injuries.
Other parasomnia activity, such as sleep terrors, can also occur in patients who are sleepwalkers.

Sleep terrors are characterized by a sudden arousal from slow-wave sleep with a piercing scream or cry, accompanied by autonomic and behavioral manifestations of intense fear. Sleep terrors manifest as a severe autonomic discharge, with tachycardia, tachypnea, flushing of the skin, diaphoresis, mydriasis, decreased skin resistance, and increased muscle tone. The patient is unresponsive to external stimuli, and, if awakened, is confused and disoriented. Amnesia for the episode occurs, although sometimes there are reports of fragments or very brief vivid dream images or hallucinations. The episode may be accompanied by incoherent vocalizations or micturition. Attempts to escape from bed or to fight can result in harm to the patient or others.

B. Sleep-Wake Transition Disorders
Rhythmic movement disorder comprises a group of stereotyped, repetitive movements involving large muscles, usually of the head and neck; the movements typically occur immediately prior to sleep onset and are sustained into light sleep. The most commonly recognized variant is headbanging, which itself has several forms. The child may lie prone, repeatedly lifting the head or entire upper torso, forcibly banging the head back down into the pillow or mattress. Headrolling consists of side-to-side head movements, usually with the child in the supine position. Bodyrocking occurs when the child rocks forward and backward without head-banging. Bodyrocking may involve the entire body, with the child on hands and knees, or it may be limited to the torso, with the child sitting. Less common rhythmic movement forms include bodyrolling, legbanging, or legrolling. Rhythmic humming or chanting may accompany any of the rhythmic movements and may be quite loud. Episodes typically occur at sleep onset, although they may also occur during quiet wakeful activities. Duration of the individual cluster of movements also varies greatly but generally is less than 15 minutes. Cessation of movements following disturbance or being spoken to suggests the occurrence of the disorder in wakefulness or lighter stages of sleep.

C. Parasomnias Usually Associated with REM Sleep
These parasomnias typically are associated with the REM sleep stage. They are grouped together because some common underlying pathophysiologic mechanism related to REM sleep possibly underlies these disorders.

Nightmares are frightening dreams that usually awaken the sleeper from REM sleep. The nightmare is almost always a long, complicated dream that becomes increasingly frightening towards the end. The long, dreamlike feature is essential in making the clinical differentiation from sleep terrors. The awakening occurs out of REM sleep. Sometimes there will not be an immediate awakening, but, instead recall of a very frightening dream will occur at a later time. This latter situation is not common with nightmares. The element of fright or anxiety is an essential part of the nightmares. Talking, screaming, striking out, or walking during the nightmare rarely occurs and differentiates nightmare from sleep terrors and REM sleep behavior disorder.

D. Other Parasomnias
This group of parasomnias comprises those parasomnias that cannot be classified in other sections.

Sleep bruxism is a stereotyped movement disorder characterized by grinding or clenching of the teeth during sleep. The disorder is typically brought to medical attention to eliminate the disturbing sounds, although the first signs of the disorder may be recognized by a dentist. Bruxism can lead to abnormal wear of the teeth, periodontal tissue damage, or jaw pain. Bruxism can also occur during wakefulness. Sleep-related and waking bruxism appear to be etiologically different phenomena, although the effects on dentition may be similar. Additional symptoms include a variety of muscle and tooth sensations, atypical facial pain, or headache. There is great variability in the intensity and duration of bruxism. These events are not usually associated with an awakening but can produce brief arousals from sleep. Although most often reported in healthy children and adults, the disorder is also commonly reported in children with cerebral palsy and mental retardation.

Sleep enuresis is characterized by recurrent involuntary micturition that occurs during sleep. Persistent bed-wetting after age five in the absence of urologic, medical, or mental pathology is considered a primary enuretic disorder. Typically, the child has never achieved continuous dry nights. In secondary enuresis, the child has had at least three to six months of dryness. Enuretic episodes occur throughout all sleep stages, as well as during nocturnal awakenings. Most episodes occur in the first third of the night. Bladder control during the daytime can be normal. Small functional bladder capacity and an irritable bladder are associated with multiple wettings at night and also with increased frequency of voiding and urgency during the day. Obstructive breathing and sleep apnea may be precipitating factors, particularly in children who have loud snoring. When obstructive sleep apnea syndrome is diagnosed, both the apnea and the enuresis often resolve after treatment of the apnea. Acquired metabolic or endocrine disorders may predispose a person to developing enuresis.

Primary snoring is characterized by loud upper-airway breathing sounds in sleep, without episodes of apnea or hypoventilation. Snoring usually produces sufficiently loud inspiratory or expiratory sounds. The snoring typically occurs while the patient is in the supine position and is usually continuous, present with each breath, and not accompanied by arousals or other evidence of sleep disturbance. The patient has no complaint of insomnia or excessive sleepiness. The patient may experience a dry mouth, which can lead to awakenings with a desire to drink water.

Infant sleep apnea is characterized by central or obstructive apneas that occur during sleep. Apnea of prematurity refers to recurrent pauses in breathing of more than 20 seconds duration or shorter pauses associated with cyanosis, abrupt pallor, or hypotonia. Two thirds of the apneic events occur during sleep, and the remainder occur during episodes of increased motor activity when infants appear awake. Cyanosis usually occurs after 20 seconds of apnea. With few exceptions, mixed and obstructive apnea terminate with spontaneous opening of the airway, and central apnea terminates with resumption of respiratory movements. Apnea of prematurity may be associated with clinically significant bradycardia. Sensory stimulation can help the infant resume ventilation. Cardiopulmonary resuscitation occasionally is necessary.

PERIODIC BREATHING   E.S. 2 weeks

PERIODIC BREATHING   A.S. f / 5 weeks
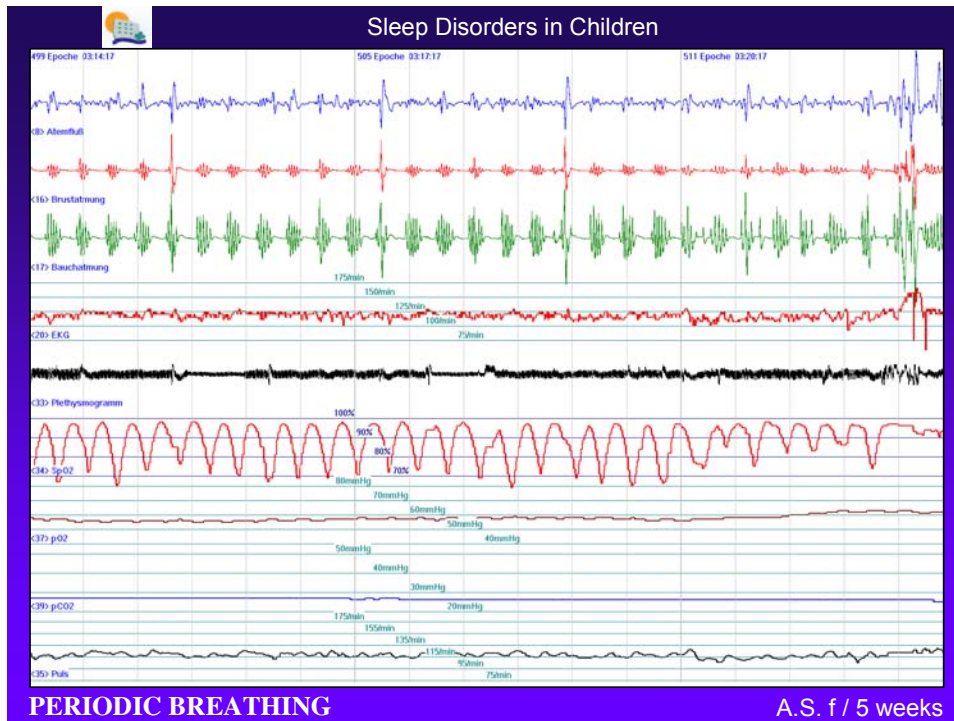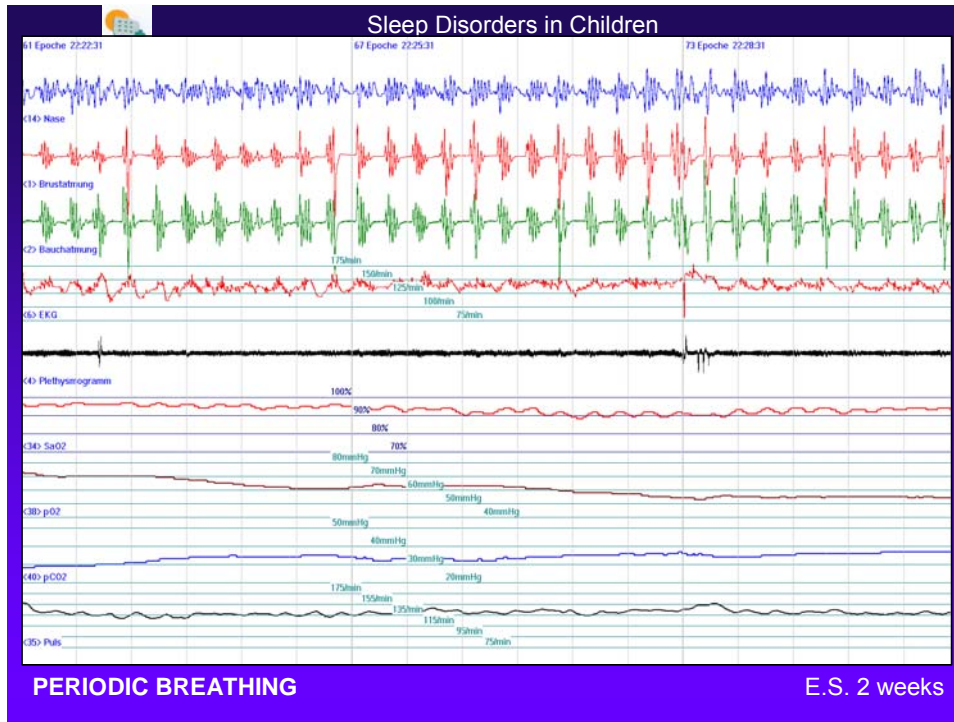
Congenital central hypoventilation syndrome (CCHS) is characterized by hypoventilation, which is worse during sleep than wakefulness and is unexplained by primary pulmonary disease or ventilatory muscle weakness. The CCHS presents in an otherwise normal-appearing infant who does not breathe spontaneously or breathes

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erratically. In most infants, a problem is evident at birth. The infant cannot be weaned from mechanically assisted ventilation. Other infants may appear to breathe adequately by clinical examination but experience hypoventilation (not necessarily apnea) that is characterized by hypoxia and hypercapnia, resulting in progressive pulmonary hypertension, cor pulmonale, and central nervous system hypoxic damage. Infants with CCHS may present with apneic episodes. Infants who present at a few months of age can have cyanosis and pulmonary hypertension as the predominant signs. Central alveolar hypoventilation can be seen in infants with myelomeningocele, the Arnold-Chiari malformation, and other neurologic syndromes due to neuroectodermal malformations involving the brain stem or craniocervical junction. There is a higher than expected frequency of neuroblastoma and Hirschsprung's disease associated with CCHS.

Sudden infant death syndrome (SIDS) is unexpected sudden death in which a thorough postmortem investigation fails to demonstrate an adequate cause for death. At least 80% of SIDS deaths occur at a time when infants were assumed to be asleep. It has not been unequivocally established whether the primary cause of death is cardiac or respiratory failure. SIDS victims are believed to have been healthy immediately before death. Temporal association with a mild upper-respiratory infection has been observed in about 60% of SIDS cases, but this finding cannot explain the death. Predisposing factors include s*leeping position, tobacco smoke exposure, preterm birth, subsequent siblings of SIDS victims, infants born to substance-abusing mothers, apnea of infancy (AOI), ethnicity and socioeconomic status.*

Benign neonatal sleep myoclonus is characterized by asynchronous jerking of the limbs and trunk that occurs during quiet sleep in neonates. The jerks usually occur in clusters of four or five, with a frequency of approximately one per second. The jerks can occur in any part of the body but most often involve the arms or legs, sometimes being most prominent in distal muscle groups. The pattern of movements tends to vary between affected individuals and can consist of flexion and extension or abduction and adduction.

4. Mechanisms through which sleep disorders affect the health of children

Sleep medicine in pediatrics is based on epidemiological data of age-dependent sleep disorders and relating environmental factors. Several studies concerning this subject have been published. Since 2002, in Germany, a group of pediatricians and child psychiatrists have been carrying out a study to evaluate sleep disorders and behavior problems in 5-6 year-old and 9-10 year-old children. The results of this study provide actual data about sleep disorders and their sequelae for the health of children. Therefore, they will be described in the following. The study has been carried out in Cologne, a German town with 1 million inhabitants. The aim was to gain data about two whole age groups of children.
6629 parents (n=8944, response: 74%) completed questionnaires about their pre-school children's sleep habits and disturbances, daytime activities and relating environmental factors during a three months period and additionally the Strengths and Difficulties Questionnaire (SDQ). In a second survey 4950 parents of 4th grade elementary-school children (n=8599, response: 58%) completed the above-mentioned questionnaires. Their children completed a modified version of both questionnaires. The X^2-test was conducted to compare means and proportions of gender specific differences in the prevalence of sleep disorders. Correlations between sleep and environmental factors as well as behavioral problems were assessed by calculating the relative risk. Under

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consideration of the big size of the sample group the level of significance was set to p<.001.

The results of the study are shown in Fig. 1-6. According to the parents, 10% of the pre-school children had sleep onset delays, 8% problems to sleep through the night, 4% daytime sleepiness, 4% sleep terrors, 3% sleepwalking, 14% nightmares, 11% nocturnal enuresis and 19% bruxism. Sleep disturbances by light and noise were mentioned by 6%, respectively 5 % of the parents. Television viewing before sleeping was reported in 57% of the pre-school children. 21% of this age group had a television set in the bedroom.

Fig. 2

Fig. 1

The data of the 4th grade elementary-school children revealed sleep onset delays sometimes in 23%, often in 6% according to the parents, problems to sleep through the night sometimes in 11%, often in 3%, daytime sleepiness sometimes in 18%, often in 1%, sleep terrors sometimes in 5%, often in 1%, sleepwalking sometimes in 7%, often in 1%, nightmares sometimes in 27%, often in 3%. According to the parents, sleep disturbances by light occurred sometimes in 6% and often in 2% of the children, by noise sometimes in 10% and often in 2%. Television viewing before sleeping was reported in altogether 81% of the 4th grade children. 34% of this age group had a television set in the bedroom.

Fig. 3

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Sleep Disorders and Behavior Problems of School-Aged German Children

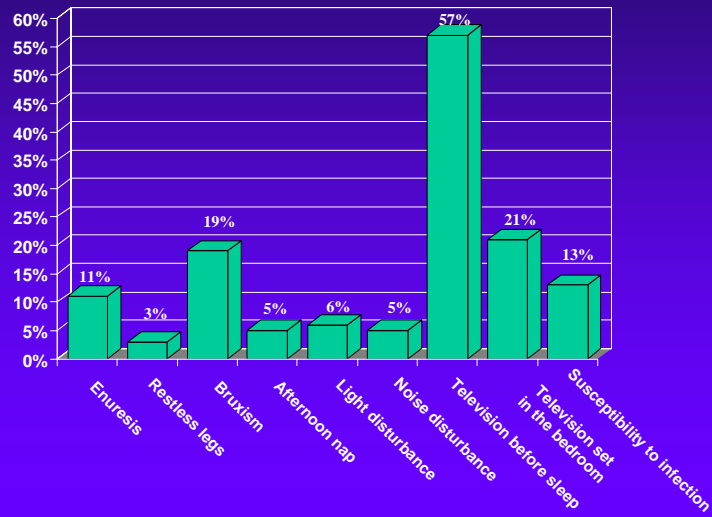Prevalence of further sleep disorders and factors of influence
Fourth grade / parents questioning 2002

Fig. 4
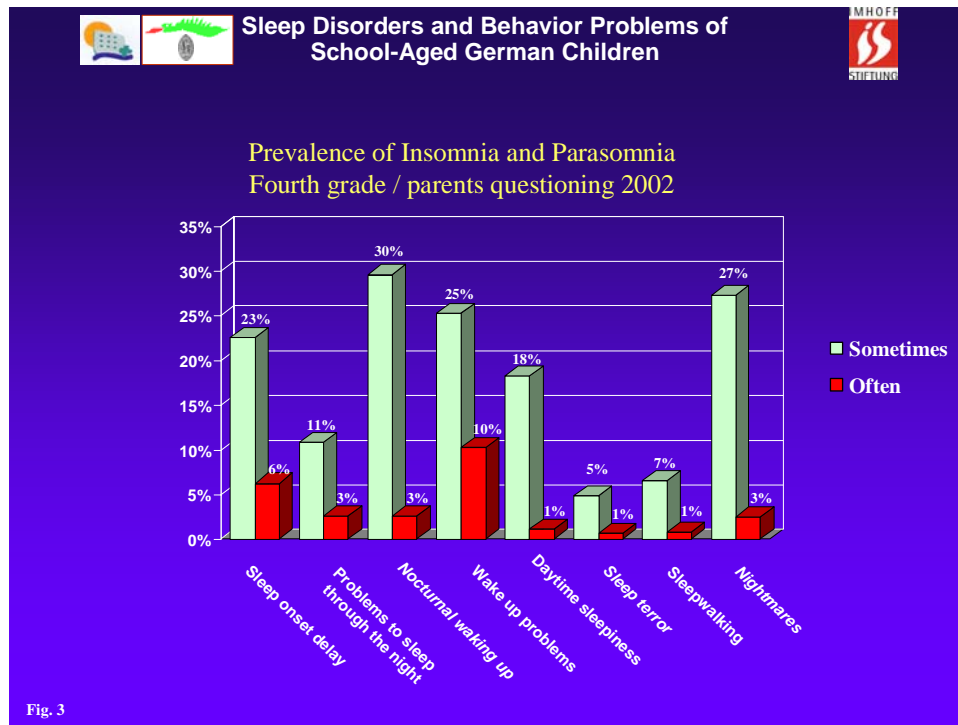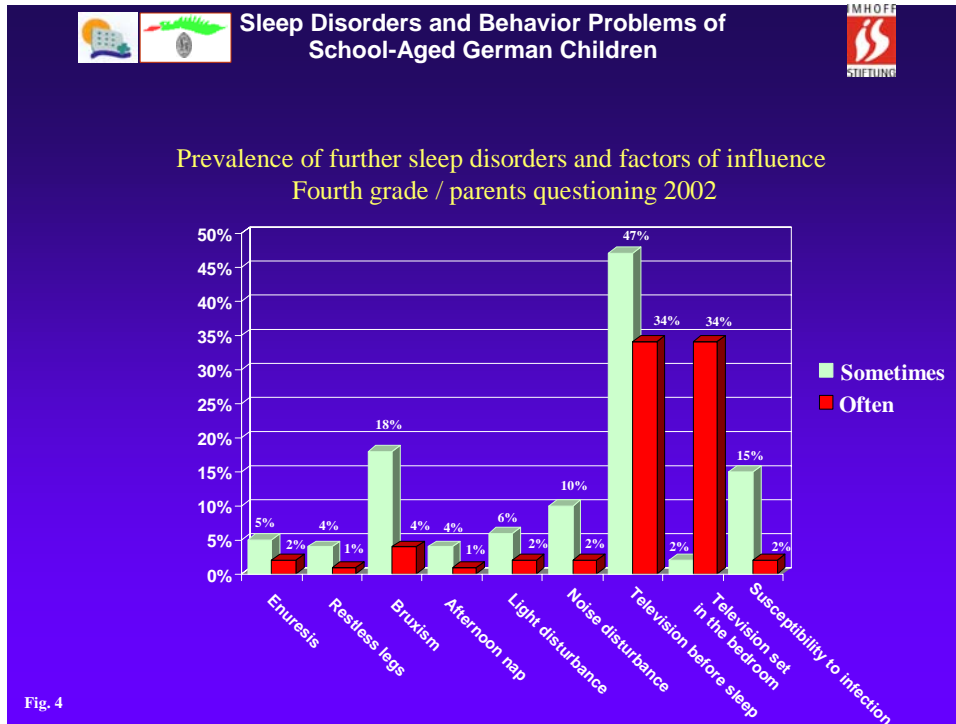
According to the children, sleep disorders appeared more often than supposed by their parents: sleep onset delays sometimes in 35%, often in 10%, problems to sleep through the night sometimes in 21%, often in 6% and nightmares sometimes in 40%, often in 4%. Sleep disturbances by light and noise were mentioned even more often by the children than by their parents: disturbances by light sometimes in 6%, often in 2%, by noise sometimes in 12% and often in 3%.

Sleep Disorders and Behavior Problems of School-Aged German Children

Prevalence of Insomnia and Parasomnia
Fourth grade / children questioning 2002

Fig. 5

Fig. 6
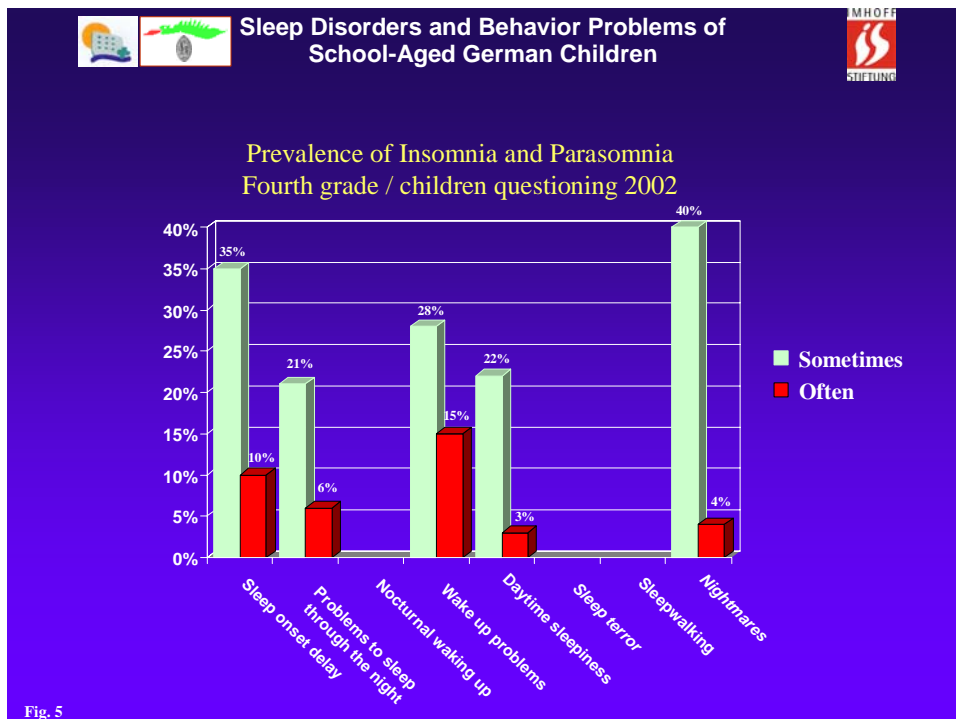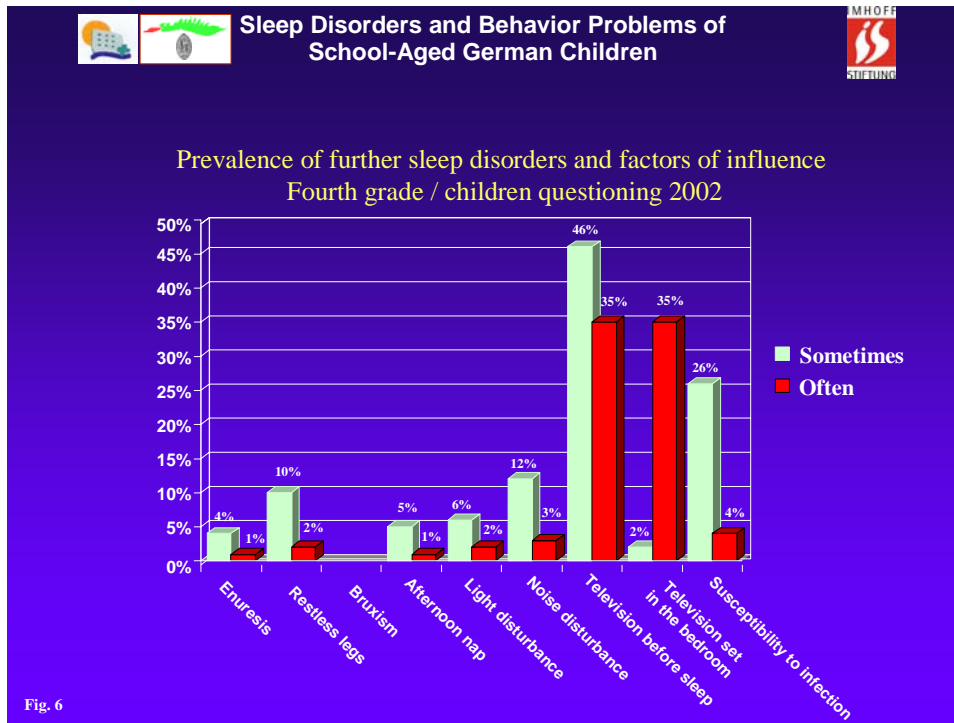
Factors associated with sleep problems are shown in Fig. 7-9. There is a strong association between sleep onset delays, problems to sleep through the night, daytime sleepiness and sleep disturbances by light and noise, infections, allergies and familiar stress. There is a strong association between television viewing before sleeping and sleep onset delays in the pre-school group and a strong association between video-playing before sleeping and problems to sleep through the night as well as daytime sleepiness in the 4th grade age group. Television viewing before sleeping in this age group, according to the children's answers, is strongly associated with daytime sleepiness. On the other hand, the risk of sleep onset delays, problems to sleep through the night and daytime sleepiness is reduced among children with regular bedtimes and regular wake times and children who wake up by themselves in the morning.

Concerning the behavior problems, assessed by the SDQ, Fig. 10 and 11 show that there are strongly increased risks of emotional problems, hyperactivity, conduct problems and peer problems among children with sleep onset problems, problems to sleep through the night and daytime sleepiness. These results are valid for both age groups.

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Sleep Disorders and Behavior Problems of School-Aged German Children

Comorbidity of sleep problems
Preschool children 2002
Relative risk for " behaviour problems " (parent`s-SDQ)

Preschool children 2002	Emotional symptoms	Hyperactivity	Conduct problems	Peer problems	Prosocial behavior
Sleep onset delay	2,6 *	3,4 *	2,8 *	2,1 *	1,3
Problems to sleep through the night	2,5 *	2,8 *	2,4 *	2,0 *	1,3
Daytime sleepiness	4,7 *	2,6 *	2,3 *	2,9 *	1,3

Fig. 10   * = relative risk for psychological problems with 99,9 % > factor 1, p < .001

Sleep Disorders and Behavior Problems of School-Aged German Children

Comorbidity of sleep problems
Fourth grade 2002
Relative risk for " behaviour problems " (parent`s-SDQ)

Fourth grade 2002	Emotional symptoms	Hyperactivity	Conduct problems	Peer problems	Prosocial behavior
Sleep onset delay	5,4 *	3,7 *	3,3 *	3,0 *	1,9
Problems to sleep through the night	4,6 *	3,2 *	3,6 *	2,0	1,2
Daytime sleepiness	4,3 *	2,8 *	5,3 *	3,4 *	3,8 *

Fig. 11   * = relative risk for psychological problems with 99,9 % > factor 1, p < .001

This study provides fundamental epidemiologic data about sleep disorders, relating environmental factors and associated behavior problems of German school-aged children. The epidemiological data corresponds to the results of the studies of Blader, Paavonen and Stein. According to these authors the prevalence of sleep onset delays among 4-12 year-old children is 11%, the prevalence of problems to sleep through the

night is 7%. Owens found sleep onset delays in 21% and problems to sleep through the night in 12% of 4-10 year-old children. Rona described sleep problems in 20% of the 5 year-old and in 6% of the 11 year-old children.

In the present study the epidemiological data of the pre-school children cannot directly be compared with the 4th grade age-group because the questionnaire for the latter group was modified. Parents and children had the opportunity to answer to the sleep-related questions with 'sometimes', 'often' and 'never', whereas the parents of the pre-school children had to choose between 'yes', 'no' and 'don't know'. The authors decided in favor of two different questionnaires, in order to gain highly differentiated results and to use directly comparable questionnaires for parents and children in the 4th grade age group. The pre-school children were not questioned themselves.

There was poor correspondence between the parent's and children's answers. The prevalences of sleep disorders and sleep associated problems were strongly higher according to the answers of the children than according to the parents' answers. This fact has also been described by Paavonen and other authors. Obviously, the parents of the 9-10 year old children don't know enough about their children's condition.

The influence of light and noise on the children's sleep can be reduced by appropriate environmental measures. Reducing infections, allergies and familiar stress situations will be more difficult. On the other hand, parents have the opportunity to make their children used to regular bedtimes and wake times from early on. There is a strong correlation between sleep disorders and behavior problems. According to the results gained, it is not possible to conclude, if sleep disorders cause behavior problems or vice versa. Probably, there is an interdependence between both.

The high prevalence of sleep disorders in childhood and the sequelae of sleep disorders to daytime symptoms should intensively focus our interest on this problem, especially as we cannot foresee, if further developmental problems are following.

5. Identification of environmental factors that may play a role in clinical sleep disorders

In the following, the interest is focused on noise disturbances during sleep. In order to evaluate the Cologne parents questionnaire, 307 telephone interviews were carried out. In this way, 61 interviews about noise disturbances were included. The results are shown in Fig. 12-17. Predominantly, parents reported on external noise. The main source of noise was the road traffic noise (66%). Mainly little and moderate sleep disturbances by traffic noise were mentioned. Also, the other noise sources, such as air traffic and rail noise caused mainly moderate sleep disturbances.

Fig. 12

Sleep Disorders and Behavior Problems of School-Aged German Children
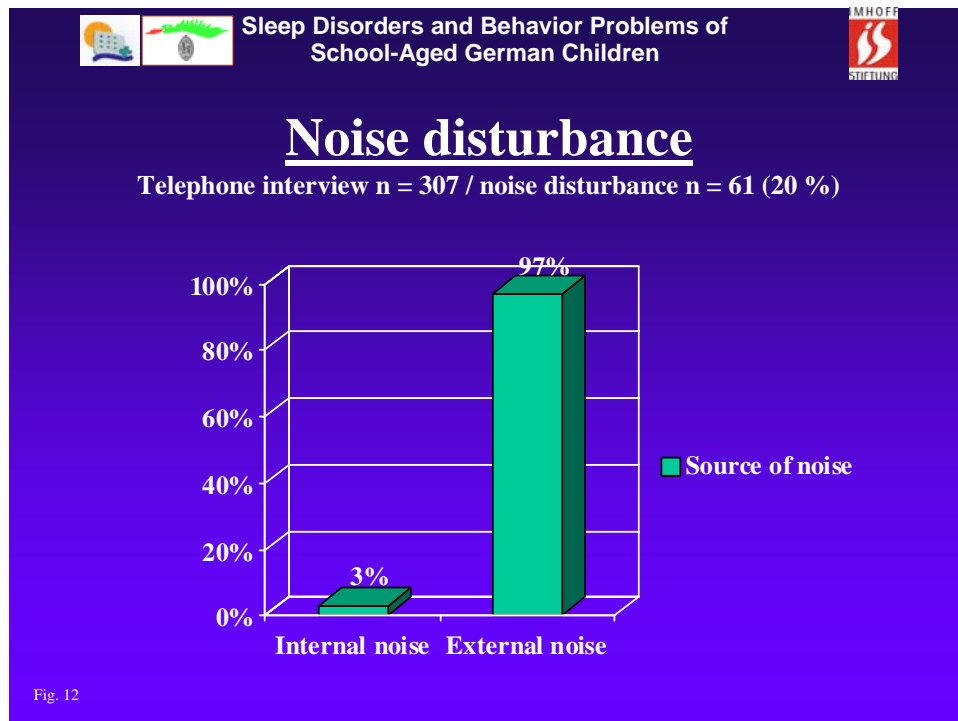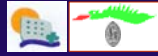
Source of noise, external noise
n = 59

Fig. 13

Sleep Disorders and Behavior Problems of School-Aged German Children
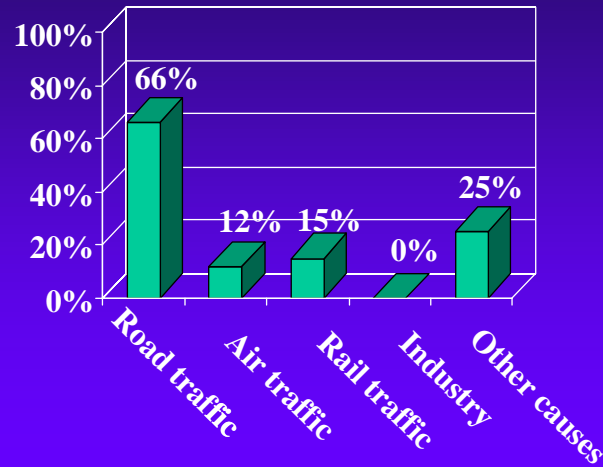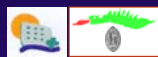
Noise disturbance road traffic
n = 39

Fig. 14

100

Fig. 15
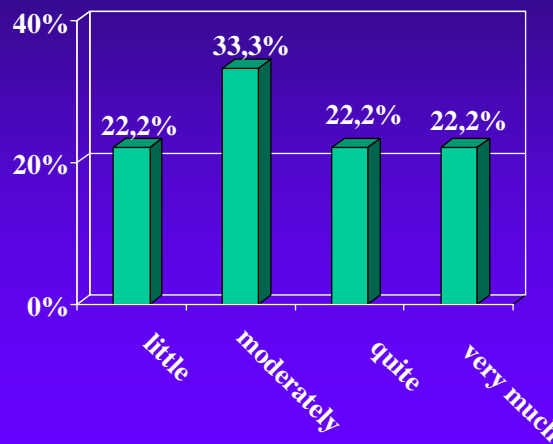
Fig. 16
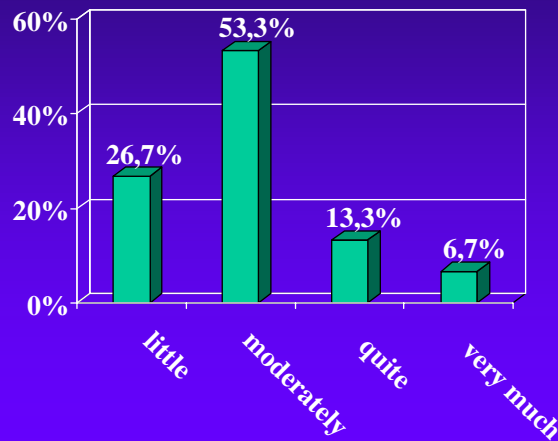
Fig. 17

Sleep disturbances by noise occur in 15% of the 9-11 year-old children. Regarding the association of sleep disorders with daytime and behavior problems it can be assumed that noise disturbances are very important in connection with sleep and health risks for children. There are few papers about noise exposure and sleep disturbances in childhood. Kahn has summarized several studies on this subject. Additionally, the study of Eberhardt should be mentioned. In this study, the effect of road traffic noise on the sleep of children is described.

Further studies are necessary. The Cologne study group has worked out a study design in cooperation with the German Aerospace Center in order to gain more specific data about noise and sleep disturbances in childhood. The realization of the study depends on sponsorship opportunities.

6. Conclusions

Sleep disorders in childhood are an important pediatric problem because of their influence on the children's health. They are also a social problem, because sleep disorders strongly correlate with behavior problems. Parents often do not recognize their children's problems and disturbances. They should concentrate more on their children's condition. Educational activities can influence regular sleep rhythms from early on and help to prevent sleep disorders. Environmental improvements can also reduce sleep disorders. The specific influence of noise on the children's sleep should urgently be examined in order to find appropriate measures for reduction. Reducing infections, allergies, and familiar stress situations will be more difficult. Finally, specific training programs for children with sleep disorders and their parents should be established. Mainly, developmental problems and any effect on future health must be prevented.

7. References

American Academy of Sleep Medicine. International classification of sleep disorders, revised (2001): Diagnostic and coding manual. Chicago, Illinois: American Academy of Sleep Medicine

Archbold KH, Pituch KJ, Panahi P, Chervin RD (2002): Symptoms of sleep disturbances among children at two general pediatric clinics. Journal of Pediatrics 40/1: 97-102

Armstrong KL, O'Donnell H, McCallum R, Dadds M (1998): Childhood sleep problems: association with prenatal factors and maternal distress/ depression. Journal of Pediatrics and Child Health 34: 263-266

Aronen ET, Paavonen EJ, Fjällberg M, Soininen M, Törrönen J (2000): Sleep and psychiatric symptoms in school-age children. Journal of the American Academy of Child and Adolescent psychiatry 39/4: 502-508

Blader JC, Koplewicz HS, Abikoff H, Foley C (1997): Sleep problems of elementary school children- A community survey. Achives of pediatric and adolescent medicine 151: 473-480

Busby, K.A., Mercier, L., Pivik, R.T. (1994): Ontogenetic variations in auditory threshold during sleep. Psychophysiology 31: 182-188

Bullinger, M., Hygge, S., Evans, G.W., Meis, M., van Mackensen, S. (1999): The psychological cost of aircraft noise for children. Zentralblatt für Hygiene und Umweltmedizin 202: 127-138

Carrol EN, Fine E, Ruff RL, Stepnick D (1995): Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 108/3: 610-618

Chervin RD & Archbold KH (2001) Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. Sleep 24/3: 313-320

Cohen, S., Evans, G.W., Krantz, D.S., Stokols, D. (1980): Physiological, motivational, and cognitive effects of aircraft noise on children: moving from the laboratory to the field. American Psychologist 35: 231-243

Dahl RE (1996): The impact of inadequate sleep on children's daytime cognitive function. Pediatric Neurology 3: 44-50.

Eberhardt, J.L. (1990): The disturbance by road traffic noise of the sleep of prepubertal children as studied in the home. Noise as a Public Health Problem. 2: 65-74

Evans, G.W., Lercher, P., Meis, M., Ising, H., Kofler, W.W. (2001): Community noise exposure and stress in children. Journal of the Acoustical Society of America. 109: 1023-1027

Gau SF & Soong WT (1995): Sleep problems of junior high school students in Taipei. Sleep 18/8: 667-673

Goodman R (1999): The extended version of strengths and difficulties questionnaire as a guide to caseness und consequent burden. Journal of Children Pschololology and Psychiatry 40: 791-799

Gontard A von & Lehmkuhl G (1997): Enuresis nocturna - neue Ergebnisse zu genetischen, pathosphysiologischen und psychiatrischen Zusammenhängen. Praxis der Kinderpsychologie und Kinderpsychiatrie 46:709-726

Fegert JM, Schulz J, Bergmann R, Tacke U, Bergmann K & Wahn U (1997): Schlafverhalten in den ersten drei Lebensjahren. Praxis der Kinderpsychologie und Kinderpsychiatrie 46:69-91

Ferber R, Kryger, M (1995): Principles and Practice of Sleep Medicine in the Child, W. B. Saunders Company

Frölich J & Lehmkuhl G (1998): Diagnostik und Differentialdiagnostik von Schlafstörungen im Kindesalter. Fortschritte der Neurologie und Psychiatrie 66: 553-569

Frölich J, Wiater, A, Lehmkuhl G (2000): Schlafstörungen bei hyperkinetisch-aufmerksamkeitsgestörten Kindern. Somnologie 4: 1-6

Haffner J, Esther C, Münch H, Parzer P, Raue B, Stehe R, Klett M & Resch F (2002): Verhaltensauffälligkeiten im Einschulungsalter aus elterliche Perspektive – Ergebnisse zu Prävalenz und Risikofaktoren in einer epidemiologischen Studie. Praxis der Kinderpsychologie und Kinderpsychiatrie 51/ 9: 675-696

Hagenah U. (2002): Schlafstörungen bei Kinder- und jugendpsychiatrischen Erkrankungen. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 30/ 3: 185-198

Hygge, S., Evans, G.W., Bullinger, M. (1998): The Munich aircraft noise study – effects of chronic aircraft noise on children's cognition and health. Congress Proceedings of Noise Effects 1998, Sydney, Australia: 268-274

Ipsiroglu O, Fatemi A, Werner I, Tiefenthaler M, Urschitz MS, Schwarz B (2001): Häufigkeit von Schlafstörungen bei Schulkindern zwischen 11 und 15 Jahren. Wiener Klinische Wochenschrift 113/7-8: 235-244

Johnson EO, Chilcoat H, Breslau N (2000): Trouble sleeping and anxiety/depression in childhood. Psychiatry Research 94: 93-102

Kahn, A. (2002): Noise exposure from various sources – sleep disturbance dose-effect relationships on children. WHO Technical meeting on exposure-response relationships of noise on health. Paper 5038933-2002/7

Klasen H, Woerner W, Wolke D, Meyer R, Overmeyer S, Kaschnitz W, Rothenberger A, Goodman R (2000): Comparing the german versions of the strengths and difficulties questionnaire (SDQ-Deu) and the child behavior checklist. Eur. Child & Adolesc. Psychiat 9: 271-276

Kraenz S, Fricke L, Wiater A, Mitschke A, Breuer U, Lehmkuhl G (2003): Schlafprobleme bei Schulanfängern. Kinder- und Jugendarzt 34/7: 562-569

Laberge L, Tremblay RE, Vitaro F & Montplaisir J. (2000): Development of parasomnias from childhood to early adolescence. Pediatrics 106: 67-74

Latz S, Wolf AW & Lozoff B (1999): Cosleeping in context: sleep practices and problems in young children in Japan and United States. Archives of pediatric and adolescent medicine 153/4: 339-346

Lehmkuhl G. (1991): Kinder in meiner Praxis. Ein Ratgeber aus der Praxis für die Praxis. Thiemann, Waltrop

Lehmkuhl G, Döpfner M, Plück J, Berner W, Fegert JM, Huss M, Lenz K, Schmeck K, Lehmkuhl U & Poustka (1998): Häufigkeit psychischer Auffälligkeiten und somatischer Beschwerden bei

vier- bis zehnjährigen Kindern in Deutschland im Urteil der Eltern – ein Vergleich normorientierter und kriterienorientierter Modelle. Zeitschrift für Kinder- und Jugendpsychiatrie: 83-96.

Mills, J.H. (1975): Noise and children: a review of literature. Journal of the Acoustical Society of America 58: 767-779

Morrison DN, McGee R & Stanton WR (1992): Sleep problems in adolescence. Journal of the American Academy of Child and Adolescent psychiatry 31/1: 94-99

Müller T & Paterok B (1999): Schlaftraining. Hoegrefe, Göttingen

Owens J, Opipari L, Nobile C, Spirito A (1998): Sleep and daytime in children with obstructive sleep apnea and behavioural sleep disorders 102/5: 1178- 1184

Owens J, Maxim R, McGuinn M, Nobile C, Msall M, Alario A (1999): Television-viewing habits and sleep disturbance in school children. Pediatrics 104/3: 1-8

Owens J, Maxim R, Nobile C, McGuinn M, Msall M (2000): Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. Archives of Pediatric and Adolescent Medicine 154: 549-555

Owens J, Spirito A, Marcotte A, McGuinn M, Berkelhammer L (2000): Neuropsychological and behavioral correlates of obstructive sleep apnea syndrom in children: A preliminary study 4/2: 67-78

Owens J, Spirito A, McGuinn M, Nobile C (2000): Sleep habits and sleep disturbances in elementary school-aged children. Developmental and Behavioral Pediatrics 21/1: 27-36

Paditz E, Gräther M, Koch R, Erler T, Hoch B, Schäfer T (1999): Häufigkeit von OSAS-Symptomen im Kleinkindesalter-Vorstudie. Multizenterstudie der AG Pädiatrie DSGM, Somnologie 3:1-6

Paavonen EJ, Aronen ET, Moilanen I, Piha J, Räsänen E, Tamminen T, Almqvist F (2000): Sleep problems of school-aged children: a complementary view. Acta Pediatrica 89: 223-228

Poustka F (1991): Die physiologischen und psychischen Auswirkungen des militärischen Tiefflugbetriebs. Huber, Bern.

Rabenschlag U (1998): So finden Kinder ihren Schlaf. Herder Verlag, Freiburg

Rabenschlag U (2000): Parasomnien im Kindesalter – Epidemiologie und klinische Bedeutung. Wiener Klinische Wochenschrift 112/5 (Suppl 2): 3-4

Remschmidt H & Schulz E (1999): Unipolare und bipolare Störungen im Kindes- und Jugendalter. In: Marneros A (Hrsg): Handbuch der unipolaren und bipolaren Erkrankungen (519-531) Thieme, Stuttgart

Richman N (1981): A community survey of one to two years-olds with sleep disruptions. Journal of the Academy of Child and Adolescent Psychiatry 20: 281-291

Riemann D & Backhaus J (1996): Behandlung von Schlafstörungen - Ein psychologisches Gruppenprogramm. Weinheim, Beltz.

Rona RJ, Li L, Gulliford MC, Chinn S. (1998): Disturbed sleep: effects of sociocultural factors and illness. Arch Dis Child 78(1): 20-25

Scholle S & Zwacka G (1997): Pädiatrische Erkrankungen - Obstruktive Schlafapnoe. In: Schulz H (Hrsg): Kompendium Schlafmedizin für Ausbildung, Klinik und Praxis/ Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (Kap. X-4.5: 1-3). Ecomed, Landsberg/ Lech

Schredl M & Pallmer R (1997): Albträume bei Kindern. Praxis der Kinderpsychologie und Kinderpsychiatrie. 46: 36-56

Schredl M & Pallmer R (1998): Geschlechtsspezifische Unterschiede in Angsträumen von Schülerinnen und Schülern. Praxis der Kinderpsychologie und Kinderpsychiatrie 47:463-476

Stein MA, Mendelsohn J, Obermeyer WH, Amromin J, Benca R (2001): Sleep and behavior problems in school-aged children. Pediatrics 107/4: 60

Stores G (2001): A Clinical Guide to Sleep Disorders in Children and Adolescents. University Press, Cambridge

Urschitz MS, Guenther A, Wolff J, Moss, DM, Urschitz-Duprat PM, Schaud, M, Poets CF (2002): Prevalence of sleep-disordered breathing in primary school children. Somnologie 6 (Suppl. 1): 30

Vela-Bueno A, Bixler EO, Dobladez-Blanco B, Rubio ME, Mattison RE & Kales A (1985): Prevalence of night terros and nightmares in elementary school children: A pilot study. Research Communications in Psychology, Psychiatry and Behavior 10: 177-188

Wiater A, Paditz E, Schlüter B, Scholle S, Niewerth HJ, Schäfer T, Erler T, Schachinger (2002): Obstruktives Schlafapnoesyndrom im Kindesalter. Deutsches Ärzteblatt 99/49: 2610-2613

Wiater A, Lehmkuhl G, Kraenz S, Mitschke A, Fricke L, Breuer U (2003): Prävalenz von Schlafstörungen bei Grundschulkindern. Somnologie 7 (Suppl. 1): 9

Wittchen HU, Krause P, Höfler M, Pittrow D, Winter S, Spiegel B, Hajak G, Riemann D, Steiger A, Pfister H (2001): NISAS-2000: Nationwide Insomnia Screening and Awareness Study. Fortschritte der Medizin 119/1: 1-11

Woerner W, Becker A, Friedrich C, Klasen H, Goodmann R , Rotheberger A (2002): Normierung und Evaluation der deutschen Elternversion des Strengths and Difficulties Questionnaire (SDQ): Ergebnisse einer repräsentativen Felderhebung. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 30/2: 105-112

Wolfson AR & Carskadon MA (1998): Sleep schedules and daytime functioning in adolescents. Child Development 69/4: 875-887

Wolke D, Meyer R, Ohrt B & Riegel K (1994): Häufigkeit und Persistenz von Ein- und Durchschlafproblemen im Vorschulalter: Ergebnisse einer prospektiven Untersuchung an einer repräsentativen Stichprobe in Bayern. Praxis der Kinderpsychologie und Kinderpsychiatrie 43: 331-339

Address for correspondence:
Dr. Alfred Wiater, Krankenhaus Porz am Rhein, Kinderklinik, Urbacher Weg 19, 51149 Köln

Medium and long term effects of sleep disturbance (by disorders and/or by stressors) on the health of adults - Sona Nevsimalova

Sona Nevsimalova

Department of Neurology, 1st Medical Faculty, Charles University, Prague,

Czech Republic

Summary
We spend almost one third of our lives sleeping, and the quality of sleep determinates the quality of our life. This presentation is focused on medium- and long-term consequences of sleep disturbances caused by different environmental stressors and by sleep disorders. Particularly sleep restriction, as the main stressor, evokes behavioral and cognitive, even neurological and other medical consequences. It is important to determine the extent to which environmental factors (e.g. stimuli evoked by noise, light, motion, temperature, high-altitude level) affect sleep quality and add to sleep loss, sleep pathology, daytime sleepiness, and daytime functioning. The aim of this paper is to follow-up the effects which the most frequent sleep disorders have on adult people's health, assuming that at least 30% of the population suffer from some sort of sleep disturbance. The greatest impact on physical and mental health is seen in patients suffering from the sleep apnoea syndrome (neurocognitive, cardiovascular, social consequences and higher mortality), from insomnia (behavioral, psychiatric and medical consequences), and from narcolepsy and hypersomnia (neurobehavioral and personality changes, medical and social consequences). Also patients suffering from the restless legs syndrome complain of neurobehavioral problems and lower quality of life, while the secondary forms of the disease are associated with other medical conditions. Parasomniacs are endangered by violent and injurious behavior during attacks that can even lead to law-actions. Behavioral, cognitive and social consequences also trouble patients with circadian rhythm disorders. Therefore, understanding the patient´s health requires equal consideration of the state of the patient awake and asleep.

Introduction
Recent advances in sleep neurobiology and in molecular biological approaches have contributed to our understanding of sleep control mechanisms in healthy sleep. Genetic expression studies of sleep in animal models have brought important discoveries about the genetic basis of sleep, and progress has been made in the electrophysiology of sleep at the neuronal level. Important roles of amino acid and monoamine mechanisms in regulating muscle tone at the motor-neuronal level across the sleep cycle have been demonstrated, and the circuitry controlling neurotransmitter release has been clarified (Dauvilliers et al. 2003). These advances contribute to our understanding of numerous sleep disorders including sleep disordered breathing, cataplexy, REM sleep behavior disorder and other parasomnias.

The neurochemical phenotypes of major groups of neurons contributing to REM and NREM sleep regulation have been identified. Previously evaluated monoaminergic mechanisms (serotonin, norepinephrine, epinephrine, dopamine, histamine) have been shown to interact with amino acid (glutamate, GABA, glycine) neurotransmitter systems at forebrain and brainstem levels. Anatomical connection between the neurons critical to REM and NREM sleep have been traced (Adrien 2003). Hypocretin/orexin has been identified as an important modulator of activity in the sleep control system. Other

peptides important in the control of sleep states have been described and localized in brainstem and forebrain sleep control regions (Dauvilliers et al. 2003).

Further physiological research is needed for the interaction between sleep and thermoregulatory, metabolic, cardiovascular and respiratory regulation at all levels of the neuroaxis to be better described and understood. The role of sex, sex hormones, sexual maturity, pregnancy and lactation in sleep control needs more detailed investigation, too.

Identification of the possible sleep indicators

Nocturnal polysomnography (PSG), usually accompanied by videorecording, is the gold standard for the detection, diagnosis (and/or for treatment monitoring) of most sleep disorders.

In spite of the availability of computerized PSG, sleep records monitoring and staging requires a skilled and educated sleep laboratory team.

A standard manual was developed to provide guidelines for sleep staging, and its recommendations are suitable for many pathologies as well (Carskadon and Rechtschaffen, 2000). One of the basic criteria of healthy sleep concerns the stability of sleep stages.

Many sleep disorders involve frequent, brief arousals that do not alter sleep stage scoring but that may be clinically relevant. Such arousals are a common feature of normal aging, but can sometimes be correlated with alertness level and regarded as a gate for insomnia. This type of arousal occurs frequently in patients with sleep apnoea syndromes, periodic movements in sleep, and other sleep disorders, and brief arousals in these cases are often associated with a body movement or respiration event. The definition of transient arousal includes any clearly visible EEG arousal (usually alpha rhythm) lasting two seconds or longer, but not associated with any stage or state change in the epoch scored. (Carskadon et al. 1982). In REM sleep transient arousals are coded only when EEG alpha activity is associated with some other sign of arousal (e.g. increased heart rate, transient changes in blood pressure, EMG elevation or respiratory irregularity). Particularly autonomic changes are highly correlated with the extent of EEG arousals. According to American Sleep Disorders Association (Chokroverty 1999) the arousal is defined as an abrupt change from a deeper stage of NREM sleep to a lighter stage, or from REM sleep to wakefulness, with the possibility of awakening as the final outcome.

Awakening is defined as a state of waking up from a NREM or REM sleep stage characterised by alpha and beta EEG activity, accompanied by a rise in tonic EMG (connected sometimes with body movements), voluntary rapid eye movements and eye blinks. Breaks in sleep, resulting in arousal and wakefulness, indicate sleep interruptions. Sleep fragmentation connotes repetitive interruptions of sleep by arousals and awakenings, leading to the interruption of any stage of sleep owing to the appearance of another stage or wakefulness, and to NREM-REM sleep cycles disruption (Chokroverty 1999). Frequent sleep pattern changes are a characteristic feature of worsened-quality sleep.

Stressors, neurobehavioral data and functional neuroimaging

According to a recent discovery (Lavie 2002), chronic partial sleep loss for as little as one week can lead to metabolic and endocrine changes as precursors for specific disease states (e.g. obesity and diabetes). Other studies have been focused on how sleep loss affects neurobehavioral functions, especially neurocognitive performance. Functional brain imaging and EEG brain mapping studies show that the pattern of functional connectivity between brain regions evident in performing specific cognitive tasks are altered by sleep loss (NCSDR, 2003). To go by this finding, the maintenance

of sustained performance during sleep loss may depend upon regional functional plasticity. Cumulative waking neurocognitive deficits and state instability that develop from chronic sleep loss have a basis in a neurobiological process that can integrate homeostatic pressure for sleep across days. Increased efforts have helped to determine the roles of REM and NREM sleep in memory consolidation.

Functional brain imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT), magnetoelectroencephalography (MEG) have been recently tested in the study of sleep and waking (NCSDR, 2003). These techniques allow measurement of metabolic and neurochemical activity throughout the brain, and can reveal dynamic patterns of regional cerebral activity during various brain states including stages of sleep and levels of alertness during wakefulness or during functional challenge. These techniques can also help identify both normal and abnormal sleep/wake processes.

In the last five years, functional neuroimaging techniques (particularly PET) have revealed that NREM sleep is associated with deactivation of centrencephalic regions (brainstem, thalamus, basal ganglia) and multimodal association cortices (e.g. prefrontal and superior temporal/inferior parietal regions). REM sleep is characterized by reactivation of all centrencephalic regions deactivated during NREM sleep except the multimodal association areas. PET studies during sleep-deprived wakefulness have revealed regional cerebral deactivations that are especially prominent in prefrontal and inferior parietal/superior temporal cortices, and in the thalamus. This pattern is consistent and helpful in explaining the nature of cognitive performance deficits that occur during sleep loss. As revealed by means of fMRI techniques during cognitive tasks performance, the maintenance of performance following sleep loss may be a function of the extent to which other cortical brain regions can be recruited for task performance in the sleep-deprived state.

PET, SPECT and fMRI studies have revealed, in depressed patients, initially elevated activation in the anterior cingulate and medial orbital cortices (NCSDR, 2003). In these patients, sleep deprivation reduces this regional hyper-activation, and improvements in mood are a function of the extent, to which this activity is reduced. These studies point to possible mechanisms by which antidepressant drugs may exert their effects. Further research should be oriented toward neuroimaging and measurements of changes in the brain´s metabolic activity at the neurotransmitter level.

Sleep, sleep restriction, environmental stressors and health consequences

According to the National Center of Sleep Disorders Research, existing U.S. government publications, such as „Healthy People 2000" and its sequel „Healthy People 2010", contain recommendations on adequate nutrition and physical fitness for healthy functioning, but no recommendation or standards for „normal" sleep duration and quality (NCSDR, 2003). Epidemiological data have never been obtained defining normal sleep and wakefulness as measured systematically. Only limited EEG sleep data as a function of age and gender are available from laboratory studies published 25-30 years ago. In spite of the importance of sleep for health and normal development and aging, there are no standards of sleep physiology based on current polysomnographic criteria. Therefore, prospective longitudinal studies are needed to develop a comprehensive database defining normal sleep-wake behavioral patterns in terms of age and sex throughout the life span.

Inspite of this fact, considerable attention has been devoted to *sleep and environmental factors* (ICSD 1997), such as sensory stimulation resulting from environmental noise, light, motion, temperature, high-altitude level and even odors.

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These environmental stimuli inhibit the initiation and maintenance of sleep. Therefore, sleep environments in which sensory stimulation is minimal (e.g. dark, quiet, comfortable temperature) tend to be preferred subjectively as a factor enhancing sleep initiation and maintenance. More attention should be paid to co-sleeping or bed-sharing, to sleep location, position and beding. Ambient noise and vibration have occasionally been studied as factors improving or impairing sleep quality, but little is known regarding the extent to which various types of noise and vibration affect sleep. A few experiments (Buresova et al. 1991) have found that light at night enhance alertness, and properly timed light exposure can speed up phase shifts of circadian biology. For example, shift workers can profit from this finding. It is important to determine the extent to which environmental factors affect sleep quality and contribute to sleep loss, sleep pathology, daytime sleepiness, and daytime functioning.

Very few data are available about stressors such as long-term hospitalization in chronically ill patients and/or critically ill patiens. Some of them spend many weeks and/or months at the acute units with severe neuropathy-myopathy syndromes caused by critically illness. However, there are no data on sleep in connection with chronic sleep deprivation due to resuscitation environment.

The health consequences of insufficient sleep have recently been studied by many sleep researchers. Approximately 40% of adults report that daytime sleepiness interferes with their work and social functioning at least a few days each month as a result of insufficient nocturnal sleep. Excessive daytime sleepiness is thus a major public health problem as a consequence of interference with daily activities including cognitive problems, motor vehicle accidents (especially at night), poor job performance and reduced productivity (Lavie, 2002). In the last decade, experimentally based data were collected on chronic restriction of sleep (by one to four hours at night), accumulating daytime sleepiness and cognitive impairment. Most individuals develop cognitive deficits from chronic sleep debt after only a few nights of reduced sleep quality or quantity; new evidence suggests additional important health-related consequences of sleep debt related to common viral illnesses, diabetes, obesity, heart disease, depression and other age-related chronic disorders.

The effects and consequences of sleep deprivation are summarized in Table 1 (according to Lavie et al., 2002).

The relationship between sleep quantity and quality as much as estimates of morbidity and mortality remain controversial. Epidemiological data (NCSDR, 2003) suggest that habitually short sleep (less than six hours sleep per night) or long sleep duration (more than nine hours´ sleep per night) is associated with increased mortality. It is not clear how the length of sleep can increase this risk. Up to now, no epidemiological prospective study has been published, examining the relationship between sleep and health (morbidity and mortality) with subjective and objective estimates. Recent studies, however, show that sleep at least eight hours long is necessary for optimal performance and for the prevention of physiological daytime sleepiness and accumulation of sleep debt.

Special attention should be paid to ***sleep and health in women***. Although sleep complaints, particularly insomnia, are almost twice as prevalent in women, 75% of all sleep research has been conducted in men. Physiologic changes in neuroendocrine hormones, body temperature, mood, and emotional state during puberty, the menstrual cycle, pregnancy and menopause have profound effects on sleep quality, daytime functioning, and well-being in women (Moline et al 2003). Although female sex is a risk factor for insomnia, and insomnia is a risk factor for depression, little is known about how changes in sex hormones during the menstrual cycle influence sleep physiology and mood. Women with significant dysmenorrhea may be at higher risk for developing

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insomnia and depression. Hormonal changes and physical discomfort are common during pregnancy, and both can affect sleep. Certain sleep disorders such as the restless legs syndrome (RLS), periodic limb movements (PLMs), sleep disordered breathing (SDB) or insomnia may emerge during pregnancy; hence, these women may face a higher risk for the above mentioned sleep disorders later in life. Pregnancy predisposes women to snoring, and pregnant women who snore may be at risk for pre-eclampsia and/or SDB. Women with pre-eclampsia and an excessive weight gain during pregnancy are more threatened with the development of SDB and pregnancy-induced hypertension. Very little is known about the effects of late stage pregnancy sleep disturbances on labor and delivery, emotional distress, or post-partum depression. Many women during the menopausal transition (perimenopause, menopause, post-menopause) complain of sleep disturbances that are attributed to vasomotor symptoms (e.g. hot flushes and night sweats) rather than to the state of menopause. Different studies show that 33-51% of women in the menopausal period suffer from insomnia, and that menopause is a significant risk factor for SDB (Moline et al. 2003).

Sleep disorders: medium and long term effects on health
The following survey of sleep disorders and their consequences covers only diseases with the most common prevalence.

Sleep disordered breathing (SDB) has come to be used as a synonym for the sleep apnoea syndrome (SAS) and related disorders. SAS is characterized by frequent cessations of breathing during sleep. It is usually associated with excessive daytime sleepiness (EDS), however, in some cases it may be associated with insomnia. Cessation of breathing during sleep can be partial (hypopnoea) or complete (apnoea), which may result more frequently from obstruction of the upper airway (obstructive apnoea), less frequently from loss of ventilatory effort (central apnoea) or a combination of both (mixed apnoea). The severity of the syndrome is determined by the rate of SDB events per hour of sleep (respiratory disturbance index, RDI or apnoea-hypopnea index, AHI) and the magnitude of associated oxygen desaturations. Both hypopnoeas and apnoeas result in arousals from sleep and lead to disrupted sleep architecture, and to the diminishing and/or disappearance of deep stages of NREM sleep and REM sleep (Lavie, 2002). A 2% prevalence of SAS is estimated in middle-aged women, 4% in middle-aged men and increases of up to 30% in the elderly.   The major consequences of obstructive sleep apnoea (OSA) are summarized in Table 2 (according to Lavie et al., 2002). Four main groups of medium and long-term effects on the SAS patients´ health can be distinguished:

1. *Neurocognitive effects:* EDS is the most common presenting complaint, being reported in up to 90% of these patients. Sleep fragmentation arising from frequent transient arousals for reopening the airway and for restoring ventilation is a characterisic polysomnographic (PSG) feature. Insufficient nocturnal sleep causes daytime sleepiness; however, EDS is reversible and will disappear with successful treatment. An increased rate of accidents due to increased somnolence is well documented, although impaired cognitive functions (e.g. judgement) can play a role, too. Cognitive performance is clearly impaired and manifested as deterioration of memory, intellectual capacity and motor coordination. The ability to perform psychomotor vigilance tasks such as visual reaction and auditory learning is also impaired. The mechanism of cognitive impairment in OSA patients is probably multifactorial and results from chronic sleep deprivation (insufficient nocturnal sleep with sleep architecture changes) and from recurrent hypoxaemia. Personality changes may also be accompanied by proneness to depression.

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2. *Cardiovascular consequences:* The most important life-threatening adverse effect of OSA pertains to the cardiovascular system. Systemic hypertension is the main risk factor. Blood pressure and percentage hypertension increase in proportion to SAS duration and severity. The level of RDI and the % decrease in nocturnal oxygen saturation are the main predictive factors of high blood pressure, both systolic and diastolic. Beside SAS, habitual snoring is another risk factor for systemic hypertension. Successful treatment of sleep apnoea helps to reduce blood pressure and other risk factors. The relationship between OSA and pulmonary hypertension is probably more complex and severe pulmonary hypertension canonly be seen in OSA patients with daytime hypercapnia (e.g., obesity hypoventilation syndrome) or with pulmonary parenchymal abnormalities (e.g. emphysema). Data published up to now give evidence of a link between sleep apnoea and higher advanced coronary artery disease and increased risk of cerebrovascular accidents. According to recent studies, mechanisms for both complications may result from OSA influence on endothelial dysfunction. A decrease in nitric oxide production and an increase in the rate of biochemical markers leading to atheroscletrosis in OSA patients have been found. A hypothesis of easier and earlier development of atherosclerosis in these patients was advanced by Lavie (2002). There are also reports of coincidence with arrhytmias in OSA patients, and of a higher risk of inflammatory and immune-mediated processes.
3. *Social consequences:* A decreased quality of life is often reported by OSA patients. The situation is influenced by day-time somnolence, decreased cognitive functions, threat of impotence in men, potential gastro-oesophageal reflux and heartburn, morning headaches and decreased self-esteem. Decreased sense of mental health and energy is often mentioned by OSA patients. The patients´ loud snoring and stops in breathing lead to decreased sleep quality in bed-partners, and affect marital relationships.
4. *Mortality:* OSA is a life-threatening factor in young and middle-aged patients, and this risk depends on the severity of the disease. RDI >20 significantly reduces the survival time of 8 compared with OSA patients showing RDI< 20. No reduced survival rate was seen in treated patients or in patients older than 50 years (Lavie 2002). Similar dependence of the mortality risk factor was observed also in patients suffering from habitual snoring and EDS. The absence of increased mortality in elderly men suggests a possible adaptation of the cardiovascular mechanisms to the long lasting nightly insults.

Insomnia is commonly defined as difficulty in initiating and/or maintaing sleep (ICSD 1997). According to a research group of the U.S. National Center for Sleep Disorders Research (1999), "insomnia is an experience of inadequate or poor quality sleep characterized by one or more of the following: difficulty falling asleep, difficulty maintaing sleep, waking up too early in the morning, nonrefreshing sleep". Insomnia also involves daytime consequences, such as „tiredness, lack of energy, difficulty concentrating, irritability." A reasonable prevalence estimate for chronic insomnia in the general population is about 10%, when considering insomnia of any duration or severity between 30% and 50%, and their incidence increases with aging. In the course of perimenopausal time, women are particularly vulnerable to developing this complaint.
The major consequences and co-morbidity in chronic insomnia (see Table 3) comprise behavioral, psychiatric and medical problems; several studies also report a higher mortality risk (Zorick and Walsh 2000).
1. *Behavioral consequences:* Transient (short lasting) insomnia is usually accompanied by spells of daytime sleepiness and performance impairment the next day. Persistent (long lasting) insomnia tends to be associated with poor performance at work, fatigue, memory difficulties, concentration problems and twice as many fatigue-related automobile accidents as in good sleepers.

2. *Psychiatric conditions:* Epidemiologic research indicates that the prevalence of any psychiatric disorder is two to three times higher in insomniacs. The risk of depression as a co-morbid state appears to be particularly strong, being approximately four times more likely in insomnia patients. Futhermore, insomnia may be an early marker for psychiatric disorders such as depression, anxiety conditions and alcohol abuse. Anxiety has been found quite common in insomniacs compared with the general population. About 25-40% of insomnia patients are estimated to have significant anxiety; the abuse of alcohol and other substances is increased in insomniacs relative to good sleepers (Ford and Kamerow, 1989). Samples of unselected psychiatric patients have about a three-fold increase in the frequency of insomnia compared with healthy control subjects, and the severity of the condition correlates with the intensity of the psychiatric symptoms. Among samples of outpatients who consulted their general practitioners for insomnia, about 50% presented with psychiatric conditions, and about half of these patients were probably depressed (Zorick and Walsh, 2000).
3. *Medical consequences:* Insomnia has been statistically associated with various medical conditions, including disorders of the cardiovascular, respiratory, gastrointestinal, renal and musculoskeletal systems. A large series of insomniacs showed that poor sleepers are more than twice as much at risk of ischemic heart disease as good sleepers (Hyyppa, 1989). Primary insomnia patients were also shown (Irwin et al.,1995) to have impaired immune system function.
4. *Mortality risk:* Only a few epidemiological studies deal with mortality in insomniacs. According to Kripke et al. (1991), reduced sleep time is a greater risk there than smoking, hypertension, and cardiac disease. Increased mortality rates are also reported in short sleepers; in this respect, though, further systematic investigation of the link between insomnia, short sleep, and death is desirable.

Narcolepsy and idiopathic hypersomnia are conditions with EDS as a leading symptom. While idiopathic hypersomnia patients (Roth, 1980, Billiard and Besset, 2003) suffer from prolonged nocturnal sleep and prolonged sleepiness during the day, accompanied very often by sleep drunkenness, sleep attacks in narcolepsy (Roth 1980, Billiard and Dauvilliers, 2003) are of short duration and the condition is as a rule combined with attacks of cataplexy (muscular atonia) provoked by emotional stimuli, and with states of hypnagogic hallucination and/or sleep paralysis. Narcolepsy, and probably also idiopathic hypersomnia are often underdiagnosed. In both conditions, diagnostic criteria require clinical history taking, and as for narcolepsy, diagnosis should include PSG examination (predominantly multiple latency sleep test, MSLT), HLA oligotyping and biochemical examination of hypocretin (orexin) levels in cerebrospinal fluid (Mignot, 2000).
Both condition have a considerable socio-economic impact on affected patients as decreased quality of life is reported by many authors (Broughton and Ghanem 1994, Nevsimalova et al. 1996, Daniels et al. 2001). The main clinical consequences (predominantly in narcolepsy) include neurobehavioral complaints, personality changes, associated medical problems and decline in social standing.
1. *Neurbehavioral complaints:* As a direct consequence of sleepiness, affected individuals are vulnerable to sleep-related accidents (road and work), tending to fall asleep in undesirable and embarrassing situations, and may therefore be prone to social maladjustment. Functional and cognitive impairment is also a characteristic feature of all conditions associated with daytime sleepiness. Although decreassed memory is reported by many patients, psychological tests show only decreased attention and concentration due to increased sleepiness, no declarative and/or nondeclarative memory changes have been reported (Nevsimalova et al., 1996, 2002).

2. *Personality changes:* Typical features of narcoleptic personality include proneness to underestimation, negative self-image and depressive disposition. Many patients suffer from increased anxiety and feelings of isolation and being misunderstood. Their affections are usually strongly guarded, but particularly in younger patients, behavioral and mood manifestations of sleepiness may include irritability leading up to violence. About half the patients present with neurasthenic symptoms and proneness to psychasthenia. The personality traits may be due to an adaptation reaction to the disease, but a biological predisposition is suspected as well (Nevsimalova et al, 2002).

3. *Associated medical problems:* Sleep apnoea may be seen more frequently with narcolepsy, an association between periodic limb movements (PLMs) and narcolepsy and/or idiopathic hypersomnia has been mentioned as well (Montplaisir et al. 2000). The effect of antidepressant treatment on these symptoms is discussed, too (Robinson and Guilleminault, 1999). Narcoleptic and hypersomniac patients suffer from autonomic nervous system dysfunction (Raynaud´s syndrome) and signs of orthostatic hypotension were described by some authors (Roth, 1980). Narcolepsy may be associated with endocrinological dysfunction; predominantly sexual functions are affected. Up to half of the patients suffers from impotency; the role of antidepressant drugs as well as autonomic dysfunction is under discussion.

4. *Social status decline:* Due to EDS, narcolepsy and hypersomnia are a major employment problem for the victims. The disorder is often a source of occupational discrimination, dismissal, early retirement, and disability. Our data (Nevsimalova et al., 2002) brought no evidence of progress at education and/or family life being adversely affected by narcolepsy. However, decreased assertion in employment and limitation in self-realization in free time were found to be an explicit consequence of the disease.

Restless legs syndrome (RLS) is a common disorder with a prevalence of some 5% of the general population and with increased incidence in older age; the disease is, however, often underdiagnosed. The main symptoms cover sensory complaints with motor restlessness predominantly in the lower extremities, worsening typically at rest and in the evening and nocturnal hours and being relieved with activity. These symptoms impair initiating and/or maintaining nocturnal sleep. Most of the cases are connected with sleep-related PLMs causing fragmentation of sleep and leading to EDS (Montplaisir et al. 2003). Idiopathic and symptomatic forms are distinguished, with a strong genetic predisposition in idiopathic cases. Table 5 illustrates the main consequences of RLS.

Recent studies (Allen et al., 2002) show that patients suffering from RLS have impaired quality of life as regards lifestyle and socio-economic status. Insufficient nocturnal sleep leads to daytime sleepiness and neurocognitive dysfunction. Secondary RLS forms are associated with other medical conditions such as iron deficiency anaemia, renal failure, rheumatoid arthritis, peripheral neuropathy and congestive heart failure. Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants are believed as underlying causes of RLS, too.

Parasomnias are a group of sleep disorders marked by undesirable physical and behavioral phenomena occurring during sleep. They are more common in children, although some of them tend to persist into adulthood or can arise even in elderly life (e.g. REM behavior disorder). Disorders of arousal such as sleep terror, sleep walking and confusional arousals affect approximately 1% of the adult population. Adult cases are typically more difficult to treat than those of childhood, and psychopathological conditions are much more frequent (Broughton, 1999). The more often described complications (Table 6) include aggressiveness and violence, light self-injury up to

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severe casualty, and odd histories describing different ways of leasing home. Violent behavior in sleep appears more frequently in men and may be related to endocrine differences (testosterone).

Sleep-wake transition disorders include benign sleep starts, sleep talking and nocturnal leg cramps. Rarely, rhythmic movement disorders can be observed in adulthood that disturb NREM, sometimes even REM sleep and lead to insufficient alertness and to day-time sleepiness.

Parasomnias associated with REM sleep, particularly the REM behavior disorder (RBD) present a great problem in the elderly. The pathophysiological abnormality in RBD is based on the absence of REM sleep atonia, which permits the „acting out" of dreams, often with dramatic and violent or injurious behavior. These acts of oneiric behavior are often misdiagnosed as manifestations of a seizure or psychiatric disorder; as a result, RBD is often underdiagnosed. RBD may be associated with underlying neurological disorders, particularly Parkinson´s disease. The overwhelming male predominance (up to 90% of all cases) points to the above mentioned relationship between sex hormones and aggression and violence. Violent behavior may result in events that have forensic implications (Mahowald and Schenck, 1999).

Circadian rhythmicity disorders are a frequent cause of sleep disruption. As for the jet lag syndrome, its short-lasting effects are better known than medium and long-lasting ones, but then, shift work and irregular sleep schedules present a great problem in modern society. Shift work insomnia is common, and impaired performance, as a primary consequence, together with the negative impact that shift work exerts on social and family life, can negatively affect the quality of life. In adition, shift work is associated with an increased risk of some somatic diseases (Mahowald and Ettinger, 1999), particularly with cardiovascular morbidity and mortality and with gastrointestinal diseases.

The advanced sleep phase syndrome (ASPS) occurs typically in older patients who habitually go to sleep early and wake up early. On the other hand, delayed sleep phase syndrome (DSPS) patients are often adolescents and/or young adults who habitually go to sleep late and wake up late. The aetiology of both conditions involves genetic and environmental factors. The most of affected individuals find these sleep patterns distressing, but some of them choose their sleep schedule to fit their life style and behavioral habits. ASPS in the elderly is often misdiagnosed as insomnia. The medium and long term effects (Table 7) are known especially in DSPS. Affected individuals suffer from chronic sleep deprivation and from behavioral and cognitive consequences of sleep debt. There is increased abuse of alcohol and other substances, and some young subjects show criminal leanings. A striking relationship has been found between circadian rhythms and psychiatric disorders, particularly seasonal affective disorder, primary depression, and bipolar affective disorder (Benca et al., 1992).

The non-24-hour sleep wake syndrome is a great problem for totally blind individuals. Complications include a large scale of neurobehavioral and social consequences caused by a lack of the ability to be entrained or synchronized by the usual time cues. Irregular sleep-wake patterns occur in individuals with central nervous system disorders (e.g. hypothalamic lesions, head injury, strokes, dementia, developmental disabilities); these can influence the clinical picture and therapeutical effect on the underlying disease.

Conclusions

Further research into the influence of environmental stressors (particularly partial loss of sleep) and into the impact that sleep disturbances have on physical and mental health is

desirable. It is necessary (1) to identify the full range of psychological, behavioral and physiological (e.g. endocrine, immune, cardiovascular, liver, muscle etc.) consequences of long-term cumulative partial sleep deprivation caused by sleep restriction and/or by insufficient nocturnal sleep in the most prevalent sleep disorders, and to clarify their underlying mechanisms, (2) to answer the question if cumulative neurobehavioral deficit that accrues during chronically restricted and/or destructed sleep is reversible, (3) to determine whether and how factors such as cognitive activity/workload and physical activity/work modulate sleepiness, (4) to determine the physiological basis and behavioral characterization of sleep inertia, and (5) to identify factors that account for individual differences in need for slep and lead to increased or decreased morbidity and mortality.

References

(1) DauvilliersY, Tafti M, Mignot E.: Molecular genetics, circadian rhythms and sleep. In: Sleep. Physiology, Investigations and Medicine. M.Billiard (ed), Kluwer Academic Plenum Publishers, New York, 2003, pp. 83-111.

(2) Adrien J.: Neurobiology of the sleep-wake cycle. In: Sleep. Physiology, Investigations and Medicine. M.Billiard (ed), Kluwer Academic Plenum Publishers, New York, 2003, pp. 31-43.

(3) Carskadon MA, Rechtschaffen A.: Monitoring and staging human sleep. In: Principles and Practice of Sleep Medicine, M.H.Kryger, T.Roth, W.C.Dement (eds), W.B.SaundersCo, Philadelphia, 2000, pp. 1197-1215.

(4) Carskadon MA, Brown ED, Dement WC: Sleep fragmentation in the erderly: relationship to daytime sleep tendency. Neurobiology of Aging 1982, 3:321-327.

(5) Chokroverty S: Glossary of terms. In: Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects. S.Chokroverty (ed), Butterworth Heinemann, Boston, 1999, pp.741-750.

(6) Lavie P, Pillar G, Malhotra A. (eds.): Sleep Disorders: Diagnosis, Management and Treatment. A handbook for clinicians. Martin Dunitz, London, 2002.

(7) National Center of Sleep Disorders Research: http:/www.nhlbi.nih.gov/health/prof/sleep/res plan/contens.html, 2003.

(8) International Classification of Sleep Disorders. Diagnostic and Coding Manual Revised. Diagnostic Classification Steering Committee, Thorpy MJ, Chairman, Rochester, Minnesota: American Sleep Disorders Association, 1997.

(9) Buresova M, Dvorakova M, Zvolsky P, Illnerova H.: Early morning bright light phase advances the human circadian pacemaker within one day. Neuroscience, Letter 1991, 121:47-50.

(10) Moline ML, Broch L, Zak R, Gross V.: Sleep in woman across the life cycle from adulthood through menopause. Clinical review. Sleep Medicine Review 2003, 7:155-177.

(11) National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: assessment and management in primary care. American Family Physician 1999, 59:3029-3038.

(12) Zorick FJ, Walsh JK: Evaluation and management of insomnia: An overview. In: Principles and Practice of Sleep Medicine, M.H.Kryger, T.Roth, W.C.Dement (eds), W.B.SaundersCo, Philadelphia, 2000, pp. 615-623.

(13) Ford DE, Kamerow DB: Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention. JAMA 1989, 262:1479-1484.

(14) Hyyppa MT, Kronholm E.: Quality of sleep and chronic illness. Journal of Clinical Epidemiology 1989, 42:633-638.

(15) Irwin M., Fortner M,Clarl C.: Reduction of natural killer-cell activity in primary insomnia and in major depression. Sleep Research 1995, 24:256.

(16) Kripke D, Simons R, Garfinkel L.: Short and long sleep and sleepiness pills. Is increased mortality associated? Archives of General Psychiatry 1991:547-554.

(17) Roth B. (ed): Narcolepsy and hypersomnia. Karger 1980.

(18) Billiard M, Besset A.: Idiopathic hypersomnia. In: Sleep. Physiology, Investigations and Medicine. M.Billiard (ed), Kluwer Academic Plenum Publishers, New York, 2003, pp. 429-435.

(19) Billiard M, Dauvilliers Y.: Narcolepsy. In: Sleep. Physiology, Investigations and Medicine. M.Billiard (ed), Kluwer Academic Plenum Publishers, New York, 2003, pp. 403-428.

(20) Mignot E.: Pathophysiology of narcolepsy. In: Principles and Practice of Sleep Medicine, M.H.Kryger, T.Roth, W.C.Dement (eds), W.B.SaundersCo, Philadelphia, 2000, pp. 663-675.

(21) Broughton R, Ghanem Q.: Socio-economic effects of narcolepsy. International Symposium on narcolepsy. June 16-17, 1994, Tokyo (Japan), Abstracts, p. 42.

(22) Nevsimalová S., Sonka K., Spacková N, Pretl M, Hofmannova R.: Narcolepsy - personality changes and social life effect. Journal of Sleep Research 1996, 5 (Suppl.1):154.

(23) Daniels E, King MA, Smith I, Shneerson JM: Health-related quality of life in narcolepsy. Journal of Sleep Research 2001, 10:75-81.

(24) Nevsimalova S., Sonka K, Spackova N, Pretl M, Hofmannova R.: Eccessive daytime sleepiness and its psychosocial consequences (in Czech). Sbornik lekarsky 2002, 103:51-57.

(25) Montplaisir J, Michaud M, Denesle R., Gosselin A.: Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving dopaminergic impairment. Sleep Medicine 2000, 1:163-167,.

(26) Robinson A., Guilleminault C: Narcolepsy. In: Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects. S.Chokroverty (ed), Butterworth Heinemann, Boston 1999, pp.427-440.

(27) Allen R, Walter A, Hening W, Mavraki E, Bell T: Factors affescting the duality of life (QoL) of adults with Restless Legs syndrome (RLS). A population-based survey. European Journal of Neurology 2002, 10 (Suppl1): 42

(28) Broughton R.: Behavioral parasomnias. In: Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects. S.Chokroverty (ed), Butterworth Heinemann, Boston, 1999, pp.635-660.

(29) Mahowald MW, Schenck CH: Sleep-related violence and forensic medicine issues. Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects. S.Chokroverty (ed), Butterworth Heinemann, Boston, 1999, pp 729-739.

(30) Mahowald MW, Ettinger MG: Circadian rhythm disorder. In: Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects. S.Chokroverty (ed), Butterworth Heinemann, Boston, 1999, pp.619-634.

(31) Benca R., Obermeyer WH, Thisted RA, Gillin JC: Sleep and psychiatric disorders. A meta-analysis. Archives of Genuine Psychiatry 1992, 49:651.

Tab. 1

Consequences of sleep deprivation

Behavioral	Sleepiness Mood changes Irritability and Nervousness	Depression /mania Violence
Cognitive	Impairment of function	Newly learned skills Short-tem memory Complex task Slow reaction time
Neurological	Mild and quickly reversible	Cerebellar ataxia, nystagmus, tremor, ptosis, slurred speech, increased reflexes, increased sensitivity to pain
Biochemical	Increased metabolic rate Increased thyroid activity Insulin resistance	Decreased weight despite increased caloric intake (in animals) Diabetes, obesity (in humans)
Others	Hypothermia Immune function impairment	Susceptibility to viral illness

Tab. 2

Consequences of obstructive sleep apnoea

Neurocognitive	Excessive daytime sleepiness, decreased cognitive performance, increased road traffic and work accidents, depression
Cardiovascular	Systemic and pulmonary hypertension, coronary artery disease, congestive heart failure, arrhythmias, cerebrovascular accidents
Social	Decreased quality of life, poor sexual function, partner´s sleep disorders, increased divorce rate
Mortality	Increased risk in young and middle age

Tab. 3

Consequences of insomnia

Behavioral	Poor performance at work, fatigue, memory difficulties, concentration problems, automobile accidents
Psychiatric	Depression, anxiety conditions, alcohol and other substance abuse
Medical	Cardiovascular, respiratory, renal, gastrointestinal, musculoskeletal disorders. Impaired immune system function
Mortality	Increased risk is reported

Tab. 4

Consequences of narcolepsy and idiopathic hypersomnia

Neurobehavioral	Sleep-related accidents (road, work), falling asleep in undesirable and embarassing situations (narcolepsy), functional and cognitive impairment, attention and concentration problems
Personality changes (narcolepsy)	Prone to underestimation, negative self –image, depression, anxiety feelings of isolation and misuderstanding. Neurasthenia, psychasthenia. Irritability, violence (young patients)
Medical	Assdociated sleep apnoea syndrome, restless legs syndrome, PLMs Autonomic nervous system, endocrinological dysfunction. Orthostatic hypotension
Social	Employment problems: job discrimination and dismissal, early etirement, disability. Limitation in self-ealization (free-time activities)

Tab. 5

Consequences of restless legs syndrome

Neurobehavioral	Increased day-time sleepiness, neurocognitive dysfunction
Social	Impaired quality of life (life style, socio-economic status)
Associated medical conditions	Iron deficiency anaemia, renal failure, rheumatoid arthritis, peripheral neuropathy, congestive heart failure

Tab. 6
Consequences of parasomnias

Disorders of arousal
    sleep terrors, sleep walking,
    confusional arousal
	Aggressive, violence injury, casualty, escape

Sleep-wake transition rhytmic movement disorder	Insufficient alertness, day-time sleepiness
REM parasomnias REM behavior disorders	Violent, injurious behaviors, law-actions

Tab. 7

Consequences of circadian rhytmicity disorders

Advanced sleep phase syndrome	Behavioral, cognitive
Delayed sleep phase syndrome	Behavioral, cognitive Abuse of alcohol and other substances Inclination to criminality Vulnerability to psychiatric disorders
Non-24-hour sleep wake syndrome	Neurobehavioral Social
Irregular sleep wake pattern	Interference with work and family activities Leading to institutionalization Discomfort for patients and those around them

Medium and long term effects of disturbed sleep on the health of children - Oliviero Bruni

Oliviero Bruni[1], Silvia Miano[2], Elisabetta Verrillo[1] and Raffaele Ferri[2]

[1] *Centro del Sonno, Dip. Scienze Neurologiche e Psichiatriche Età Evolutiva*
University of RomeLa Sapienza, Italy

[2] *Centro del Sonno, U.O. Neurologia I.C*
IRCCS Oasi Maria SS, Troina (EN), Italy

Address for correspondence

Oliviero Bruni, MD
Center for Pediatric Sleep Disorders
Dept. Developmental Neurology and Psychiatry
Univ of Rome "La Sapienza"
Via dei Sabelli 108 - 00185 - Rome (Italy)
TEL. +39 06 44712257
FAX +39 06 4957857
E-mail: *oliviero.bruni@uniroma1.it*

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Executive Summary

This report will focus on the developmental consequences and health risks associated with disturbed sleep and describe the existing knowledge on the health impact of sleep disturbances that may be considered as similar to those caused by noise.

- Sleep disorders during childhood represent an important children's health issue
- Children are more vulnerable than adults to effects of disturbed sleep
- Sleep disturbances may affect cognitive development and learning during a critical brain growth period
- Environmental noise at home during night time could lead to sleep disruption without leading to behavioral awakenings through the alteration of sleep microstructure, in a similar manner as other sleep disturbing events such as respiratory disturbances
- Sleep disruption and/or sleep fragmentation (mainly in SWS and REM) is the common physiopathological mechanism involved in the daytime consequences of different sleep disorders
- Children with disturbed sleep presented cognitive dysfunction and behavioural disturbances, abnormal growth hormone release, increase of diastolic blood pressure that are all related to sleep fragmentation
- A major issue is that children who have experienced prolonged sleep disruption during a period traditionally associated with major brain growth and substantial acquisition of cognitive and intellectual capabilities may suffer from a partially irreversible compromission of their potential for academic achievement
- In children, indicators of sleep disruption such as behavioral awakenings evaluated by actigraphs or sleep architecture abnormalities are not sufficient to evaluate correctly the consequences on growth, cognition and behavior in children
- In children the more stable homeostatic process of sleep does not permit a clear sleep macrostructural disruption, the arousal threshold is higher and EEG arousals are less common in children than adults while subcortical arousals occur frequently
- The potential indicators of sleep disruption in children are mainly represented by arousals and cyclic alternating pattern (CAP)
- Arousal analysis, CAP analysis and identification of new parameters of sleep fragmentation (Sleep pressure score) in children can give new insights on the relationships between sleep disruption and cognitive consequences

I. Introduction

Sleep disorders during childhood such as disorders of initiating and maintaining sleep, disorders of excessive somnolence, circadian rhythm abnormalities, sleep breathing disorders and disturbed sleep due to medical conditions or environmental factors such as noise, represent an important children's health issue.

In the last years, a growing body of literature demonstrated the strict relationships between sleep disturbances and daytime consequences, especially related to the cognitive-behavioral functioning.

This report will focus on the developmental consequences and health risks associated with disturbed sleep and describe the existing knowledge on the health impact of sleep disturbances that may be considered as similar to those caused by noise.

The document takes into account several papers published on the effects of the sleep disruption on health and on quality of life during childhood and has the aim to evaluate the medium- and long-term effects of disturbed sleep on health and to identify the possible indicators of negative consequences on health.

II. Background

In the past and for a long time it has been assumed that body restoration occurs mainly during NREM sleep and brain restoration mainly during REM sleep. However, this view is not acceptable any more; recent studies showed that memory and learning mechanisms need not only REM sleep but also NREM sleep preservation.

Sleep disruption and/or fragmentation is the common physiopathological mechanism involved in the daytime consequences of different sleep disorders and, therefore, might be responsible for several health problems that cannot be easily recognized as primarily due to sleep disturbances (Hobson and Pace-Schott, 2002).

Sleep is commonly referred to as a condition of isolation and detachment from the outside world. It is the period of our daily life during which the responses to extrinsic stimuli are abolished or drastically attenuated. However, the sleeping brain may be promptly aroused. During sleep, information processing can occur with some particularly meaningful stimuli, such as subject's name (Oswald et al., 1960; McDonald et al., 1975) and the physiological responses to noise during sleep mostly reflect the magnitude of the auditory stimuli (Di Nisi et al., 1990).

There is increasing evidence from both experimental data and everyday life that sleep organization is extremely sensitive to acoustic stimuli. The tolerable limits and the awakening thresholds mostly depend on the functional state during which the noise occurs, as emerges from the hierarchic reactivity of the sleep stages under auditory tests (Rechtschaffen et al. 1966). Anyway, apart from its physical pattern (i.e., amplitude, spectrum, intensity) and psychological content (Oswald et al. 1960), noise generally exerts an arousing influence on sleep (Ehrhart and Muzet 1974; Muzet and Naitoh 1977).

In polygraphic terms, a noisy night-time environment causes a decrease in delta sleep (Stage 4 NREM) and in REM sleep and to an increase in the time spent awake (Vallet and Mouret 1984).

The lack of habituation and the remarkable improvement after noise abatement (Bistrup ML, 2003) suggest that the environment is continuously scanned for potential danger and that noise represents in any case a stressful factor.

Effects of noise on sleep in children

Environmental noise represents one of the underestimated causes of sleep disruption. In modern countries and in high industrialized societies there is a transition of environmental health dangers with economic status with an increase of so-called "modern risks" for health. One of the most important factors is environmental noise. Noise pollution constitutes a persistent problem that threatens to increase significantly in the future. Nearly half of the World Health Organisation European region is exposed to daily community noise levels of between 55 and 65 adjusted noise levels (dBA) that exceeds recommended criteria for residential areas, schools, and hospitals (Berglund et al., 2000).

Children may be more vulnerable to noise than adults, because of poorer control over their environments. Therefore, in apparent contradiction to general belief, children react to night-time noises.

The report from a project coordinated by the National Institute of Public Health of Denmark in 2001 by Marie Louise Bistrup, has identified as future research priorities the effects of noise on children's sleep and cognitive functions. In this paper on page 19-20 it is stated: *"The effects on children's cognitive capacity and the role of noise on stress*

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and on sleep as well as awareness of children's circadian rhythms, psychologically as well as physiologically, need to be considered when the public health of children is assessed with regard to noise." This statement, it is more and more important considering the recent reports on the link between sleep and cognitive-behavioral functioning (Hobson and Pace-Schott, 2002).

Most of the studies on the negative effects of noise on cognitive-behavioural functioning focused on major noise sources (airports or highway traffic) neglecting typical neighbourhood noise (Haines et al., 2001; Haines et al., 2003) and concentrated on the impact of daytime noise during school hours, ignoring the noise level at night (Bistrup, 2003).

However, a number of reports showed that physiological responses occur in children at lower levels of noise exposure than in adults. Children aged 5 to 7 years, reacted with changes in their respiratory curves to acoustic stimuli of much lesser intensity (10 to 15 dB) than adults did (Smeczuk, 1967). However, considering behavioral parameters such as awakenings, children appear to be less easily awakened than adults during Slow Wave Sleep (SWS) and behavioural awakenings are nearly absent in situations in which adults do show that they are awake, with a behavioural response (Lukas, 1972).

Another study showed that in 24 boys, aged 8-12 years, noise can affect sleep differently depending on sleep stage: behavioral arousals occurred in 35% of cases in stage 2 NREM and in 49.8% during REM sleep, while only 4.6% occurred during SWS (Busby and Pivik, 1985).

Eberhardt (1988) studied the effects of road traffic noise on sleep in children (aged 6 - 11 years) by using EEG recordings, actimetry (body movements) and questionnaires: children living in quiet surroundings were exposed to on average 68 pre-recorded truck noises with maximal sound levels of 45, 55 and 65 dB(A) during several nights and showed: a) increased body movements; b) very few awakenings; c) no statistically significant changes in any of the EEG parameters studied, but an increase in intermittent wakefulness. Eberhardt (1988) concluded that children are less sensitive to noise-induced awakenings and body movements than adults.

Noise exposure during daytime and night time and its relationships with mental health

Passchier-Vermeer (2001) in evaluating studies of stress-related somatic effects on blood pressure and neuroendocrine indices of chronic stress in schoolchildren raised the problem that noise exposure during class and exposure at home are probably highly correlated. Therefore he raised the following problems/questions: noise-induced effects should be exclusively attributed to noise exposure during class or exposure in other situations (at home) also influenced the effects observed? And what is the role of noise during sleep in the cognitive effects of noise exposure on children, since sleep disturbance caused by night-time noise can impair memory reprocessing during sleep?

To investigate the relation between typical environmental noise levels (highway, rail, road) and multiple mental health indices of school children, Lercher et al. (2002) carried out a study in a demarked area defined by the Austrian Government as an environmental health impact assessment. They demonstrated noise effects on children's mental health at low typical levels of environmental noise: in general, exposure to ambient noise was associated with small decrements in children's mental health and poorer classroom behaviour. Child self reported mental health was significantly linked to ambient noise only in children with low birth weight and preterm birth.

In a recent survey on sleep hygiene in 818 preschoolers and school-aged children it has been found that subjects living in a noisy environment had shorter sleep duration and

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later bedtime. Further, significant differences in several sleep behavior scales as evaluated by the Children Sleep Habits Questionnaire (Owens et al., 2000) have been found: children living in noisy environment showed higher scores in the following scales: sleep onset delay, sleep duration, parasomnias and sleepiness. Also, noisy environment was reported in 21% of the children with sleep problems vs. 8% of controls (Giannotti et al., 2004).

Environmental noise experienced at home during night time is an unpredictable and most often discontinuous event (i.e., traffic noise, aircraft or train noise, noisy environment for other reasons i.e. proximity with a discotheque, etc.), that might lead to sleep disruption without leading to behavioral awakenings through the alteration of sleep microstructure, in a similar manner as other sleep disturbing events such as respiratory disturbances.

Therefore, considering clinical settings, we can assume that, in children, an experimental model of consequences of noise can be represented by the respiratory disturbances during sleep such as snoring, upper airway resistance syndrome (UARS) or obstructive sleep apnea (OSA), either for the noise produced by snoring or by the effects on arousal system and sleep microstructure.

For this reason, we will describe the well-studied effects of sleep breathing disorders on children's health and then we will evaluate the indicators of sleep disruption from the point of view of sleep microstructure.

III. Neuroanatomical basis of the relationships between sleep, behavior and learning

Behavioral-cognitive disturbances consequent to sleep disruption are mainly related to memory and executive functioning. Executive dysfunction is a primary manifestation of the adverse cellular and biochemical events triggered by OSA, and is anatomically related to dysfunction of prefrontal regions of the brain cortex (PFC). Harrison and Horne (2000) have argued that sleep-deprived adults display PFC-related cognitive dysfunction. Furthermore, Dahl et al. (1996) have also applied a PFC model to account for the relationship between sleep disruption and emotional disturbances in children.

Model linking prefrontal cortex, sleep and cognitive dysfunction in children

Beebe and Gozal (2002) described a model for explaining the behavioral-cognitive complications seen in sleep disruption due to OSA, involving the PFC and the executive system (composed of behavioural inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis, and contextual memory).

Whereas the majority of other structures of the brain are silent at some point during sleep, the PFC displays reduced activity across all sleep stages. The PFC appears functionally disconnected during sleep from other regions with which it normally interacts during daytime hours, because of the necessity for `recalibration' of PFC circuits without input interference from other brain regions. Functional neuroimaging and magnetic resonance spectroscopy have documented changes in prefrontal metabolism and neurochemistry following sleep deprivation in healthy adults (Maquet, 2000). Sleep may be the only time when PFC restoration is possible, and it is reasonable to assume that disruption of sleep continuity can modify this homeostatic process.

The PFC is one of the last areas of the brain to mature, with some functional components not completing maturation until adolescence or even later. Though PFC-mediated behaviors are evident as early as infancy and preschool years, children do not reach adult levels on many executive functional tasks until age of 10-12 years. Ongoing researches suggest that the PFC is particularly vulnerable to the cyclical hypoxia of OSA, and that the peak period of OSA incidence in childhood may constitute a period of particular susceptibility to disruption in PFC that may be only partially reversible, despite increased maturational plasticity.

Moreover, the cognitive and behavioral effects of OSA may directly impact on the child's learning and social development and there is some evidence that residual learning deficits may occur long after sleep-disordered breathing has resolved in children.

Executive functioning deficits, in the adults, correlate better with the level of blood gas abnormalities and sleep fragmentation than with either self-reported or objectively measured sleepiness. In OSAS children hypoxemia is not as evident as in adults; therefore we can suppose that neurobehavioral and cognitive dysfunctions at this age are mainly related to sleep fragmentation (i.e. cortical and subcortical arousals).

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IV. Neurophysiological basis of the relationships between sleep, behavior and learning

Several studies have pointed out the role of sleep for brain maturation and psychomotor development in infants and children.

Sejnowski and Destexhe (2000), in order to evaluate the functions of sleep, analyzed the patterns of the brain rhythms during normal sleep. The thalamus is the major gateway for the flow of information toward the cerebral cortex during sleep. During spindling and slow-wave sleep, the thalamo-cortical neurons increase activity that are more spatially and temporally coherent than in the awake state. For example, spindle oscillations induce calcium to entry in the dendrites of pyramidal neurons, that later could lead to permanent changes in the network. Thus, calcium entry during sleep may be the mainly factor which prepare the synapses for permanent changes, and also may activate a molecular 'gate', opening the door to gene expression.

SWS and spindle oscillations in memory consolidation

In analyzing the spatiotemporal structure of SWS oscillations, they stated that the most interesting observation was that slow-waves also contain a myriad of brief episodes of low-amplitude fast oscillations (similar to those occurring during wake) that are nested within slow-wave complexes. These electrophysiological brief episodes are equal to the fast oscillations of awake and REM sleep. SWS could then be part of 'recall' and 'store' sequences, in which the fast oscillations could reflect recalled events experienced previously, which are stored in the network through the synchronized firing that occurs during the slow-wave complexes in the EEG. SWS could be viewed as a cyclic, iterating process leading to memory consolidation.

These two types of sleep oscillation, spindles and slow waves, may have complementary roles in network reorganization. At sleep onset, the thalamus generates synchronized spindle oscillations. This process could serve to open the door between synaptic activation and gene expression, so that pyramidal neurons are ready to produce permanent changes in response to some specific synaptic events that need to be consolidated. As sleep deepens, slow-waves such as delta oscillations progressively dominate the EEG. Alternating slow-wave complexes with brief episodes of fast oscillations during slow-wave sleep could bring to the permanent formation of small sets of strongly interacting neurons. This type of interactions might provide a biophysical mechanism for the consolidation of memory traces in cerebral cortex: sleep spindle oscillations might have a prominent role in gating mechanisms for plasticity in pyramidal neurons, and in a subsequent phase of sleep the slow waves and fast oscillations could provide the substrate for consolidation.

Hippocampus and neocortex interactions in information processing

Moreover, this mechanism might involve interactions between the hippocampus and the neocortex. The hippocampus may not be the site of storage for the information before consolidation, but may instead facilitate the associative links between information stored in different parts of the cerebral cortex and other parts of the brain.

During waking, environmental input to the primary sensory neocortices proceeds into the hippocampus, during NREM, information from the hippocampus to the neocortex and

during REM, wake-like flow of information from neocortex to hippocampus as in waking (Maquet et al., 2000). The neocortex during the wake state provides the hippocampal formation with a detailed description of the days events; during slow-wave sleep, the inputs from the hippocampus recreates some version of these events in the neocortex, where permanent memory representations are gradually formed over repeated episodes of sleep. When the neocortex switches from slow-wave sleep to REM sleep characterized by high-frequency oscillation of 40 Hz, similar to that which occurs during attentive waking states, the hippocampus switches from sharp wave activity to a theta rhythm. This cycle of reciprocal activation and reactivation occurs repeatedly during sleep (Sejnowski and Destexhe, 2000).

Dual process hypothesis of sleep for memory and learning

Other authors (Peigneux et al., 2001) confirmed the role of sleep in the processes of memory consolidation and pointed out the importance of NREM sleep also for cognitive functioning. They proposed the dual-process hypothesis that NREM and REM sleep facilitate different memory processes:

a) NREM sleep facilitates declarative or explicit memory (deprivation of early-night, SWS-rich, sleep selectively impairs performance on declarative-memory tasks such as paired-word associates or spatial-task memory)

b) REM facilitates procedural and non-declarative learning (deprivation of late-night, REM-rich, sleep impairs performance on procedural-memory tasks, i.e. mirror drawing or word-stem priming)

These two processes are strictly related: improvement in a discrimination task performance was found to correlate with the % of slow-wave sleep in the first quarter of the night and the % of REM sleep in the last quarter indicating a two-stage process for the consolidation of improvement on this task (Stickgold et al., 2000).

Therefore the disruption of either SWS or REM can lead to negative daytime consequences on mental health. Different studies have demonstrated that mainly SWS in the first part of the night and REM are the most affected sleep stages after noise exposure (Terzano et al., 1990, Lukas, 1972). Therefore we can hypothesize that the negative effects of noise during sleep can be mediated by SWS and REM fragmentation. Further, it is not necessarily needed that the duration of sleep stages are reduced in order to have negative consequences but the alteration of their continuity can have the same negative effects.

V. Medium and long term effects disturbed sleep

In the literature few data on medium and long term effect of disturbed sleep in children is available form the longitudinal point of view. Most reports focused on respiratory disturbances during sleep as theoretical model to evaluate long term effect of disturbed sleep in children. In this review we will report the medium and long term negative consequences of disturbed sleep on cognitive functioning, behavior, mental health, growth and cardiovascular system.

Neurocognitive manifestations

Several studies in adults have shown that sleep fragmentation and hypoxemia can result in daytime tiredness and loos of concentration, retrograde amnesia, disorientation, morning confusion, aggression, irritability, anxiety attacks and depression. One could hypothesize that sleep fragmentation and hypoxemia would affect the neuropsychological and cognitive performance also in children, where the impact of abnormal sleep may be even greater than in adults. In fact, neurocognitive and behavioural deficits and school problems have been reported recently in children with sleep related obstructive breathing disorders (SROBD).

Attentional capacity

This represents the ability to remain on task and appropriately attend to stimuli in the environment. Taken together the studies to date indicate that children with SROBD are less reflective, more impulsive, and show poorer sustained and selective attention. Blunden *et al.* (2000) reported that, compared to sixteen controls, sixteen children with mild SROBD showed reduced selective and sustained attention. Owens-Stively *et al.* (1997) suggested a dose response in attention-impulsivity with moderate-severe OSAS children showing greater deficits than mild OSAS children. Importantly, early treatment showed that attention deficits in children with OSAS are reversible (Guilleminault *et al.* (1982)). In another study, 12 children with moderate to severe OSAS showed significant post surgical reductions in inattention and improvement in aggressive and hyperactive behaviors and vigilance after surgical treatment (Ali et al., 1996).

Memory

Rhodes et al. (1995) found inverse correlations between memory and learning performance and the apnea hypopnea index in 14 morbidly obese children. Smaller deficits were observed by Blunden et al. (2000), who found in their sample of children with mild SROBD that mean global memory performance was in the lower end of the normal range compared to controls.
A recent study using actigraphy in normal school-age children showed that lower sleep efficiency and longer sleep latency were associated with a higher percentage of incorrect responses in working memory tasks; shorter sleep duration was associated with performing tasks at the highest load level only. Also, controlling for age, gender, and socioeconomic status, sleep efficiency and latency were significantly associated with the mean incorrect response rate in auditory working memory tasks. This study showed that **s**leep quality (evaluated as sleep efficiency= 100* [sleep + light sleep]/duration) is more strongly associated with performance in working memory tasks than sleep duration,

suggesting that in assessing sleep, attention should be directed not only at the amount of sleep but also at sleep quality.

Intelligence

Inspection of the mean IQ scores reported in the study by Rhodes et al. (1995) suggested that their sample of five obese children with moderate-severe OSAS performed in the borderline range whereas controls performed in the normal range. Blunden et al. (2000) showed smaller deficits in children with mild SROBD whose mean verbal and global IQ were in the lower end of the normal range.
It remains unclear as to whether the putative negative effects of SROBD on intelligence are global in nature or confined to specific areas such as verbal rather than performance or visuo-spatial intelligence and whether these impairments can be reversed.

Learning and school performance

It has been widely reported (Stradling et al., 1990; Guilleminault et al., 1996; Richards et al., 2000) that children with SROBD show reduced academic performance and learning. Weissbluth *et al.* (1983) found that poor academic achievers had a higher prevalence of night-time snoring (38% vs. 21%) and breathing difficulties (13% vs. 6%). Forty percent of 297 children with SROBD (22% primary snorers and 18% sleep-associated gas exchange abnormalities) were in the lowest 10th percentile of academic performance (Gozal, 1998) and SROBD in early childhood may continue to adversely affect learning in later years (Gozal and Pope. 2001). Gozal (1998) found in his sample of poor academic achievers that school grades improved post-adenotonsillectomy in treated but not untreated children.
Apart from SROBD, also healthy normal children with fragmented sleep (measured by actigraphy) showed lower performance on neurobehavioral functioning (NBF) measures, particularly those associated with more complex tasks and also had higher rates of behavior problems (Sadeh et al., 2002). Further, in normal children, without sleep disorders, also modest sleep restriction can affect children's NBF. Sadeh et al. (2003) monitored 77 children for 5 nights with activity monitors; on the 3rd evening, the children were asked to extend or restrict their sleep by an hour on the following 3 nights. Their NBF was reassessed on the 6th day following the experimental sleep manipulation and showed that sleep restriction led to improved sleep quality and to reduced reported alertness.
These studies suggest that fragmented sleep or insufficient sleep is highly relevant during childhood and that children are sensitive to modest alteration of their natural sleep duration.
Early reports documented that untreated OSAS can have long term negative effects such as failure to thrive, cor pulmonale, and mental retardation. These severe sequelae are less common now, due to the early diagnosis and treatment, but recent reports focused on other long term effects mainly related to neurocognitive deficits, such as poor learning, behavioral problems, and attention deficit hyperactivity disorder (Marcus, 2001).
Gozal et al. (2001) tried to determine the potential long-term impact of early childhood snoring. Analyzing questionnaires of 797 children in low academic performance group (LP) and 791 in high academic performance (HP) group, they found that frequent and loud snoring during early childhood was reported in 103 LP children (12.9%) compared with 40 HP children (5.1%). Therefore, children with lower academic performance in middle school are more likely to have snored during early childhood and to require

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surgery for snoring compared with better performing schoolmates. These findings suggest that children who experienced sleep-disordered breathing during a period traditionally associated with major brain growth and substantial acquisition of cognitive and intellectual capabilities may suffer from a partially irreversible compromise of their a priori potential for academic achievement. Three major components that result from the intermittent upper airway obstruction that occurs during sleep in children could theoretically contribute to such neurocognitive deficits, namely episodic hypoxia, repeated arousal leading to sleep fragmentation and sleep deprivation, and periodic or continuous alveolar hypoventilation.

Schooling problems may underlie more extensive behavioral disturbances such as restlessness, aggressive behavior, excessive daytime sleepiness, and poor neurocognitive test performances. Nearly 20-30% of children affected by OSAS or loud and frequent snoring have important consequences on behavior with inattention and hyperactivity. Problems similar to symptoms of ADHD are linked to the presence of repeated sleep arousals, and intermittent hypoxic events, inducing a lack of behavioral inhibition, with negative implications for working memory, motor control, and self-regulation of motivation and affect.

In contrast with these data, recently Friedman et al. (2003) found a significant improvement of functions, at least in mild to moderate OSAS, when measured several months following after adenotonsillectomy, but they confirmed that their results could not be rule out the possibility of partial irreversible damage to academic function even after treatment that may be detected only later in life and stated that also adults with deficits of neurocognitive executive functions related to the prefrontal area failed to improve significantly after treatment.

The negative long term effects may be mediated by the irreversible alteration of PFC and be related to structural changes of the brain as a consequence of both hypoxemia and sleep fragmentation induced by OSAS or other pathologies affecting sleep.

In a recent report Macey et al, (2002) demonstrated, in OSAS adults, gray matter loss in cerebral sites involved in motor regulation of the upper airway as well as in areas contributing to cognitive function (frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum). It can be argued that, in critical stages of brain development (i.e. in childhood), such effects can determine even more severe consequences that could explain the negative long term effects.

It is speculative to think that the remodeling of brain could be also mediated by sleep and therefore sleep fragmentation could affect the process of brain plasticity (i.e. the capacity of the brain to modify its structure and function along time). Recent studies showing experience-dependent gene-expression of gene zif-268 during paradoxical sleep in rats exposed to a rich sensorimotor environment or the role of sleep for enhancing the remodelling of ocular dominance in the developing visual cortex are also in line with the hypothesis that sleep participates to neuronal plasticity and memory processes (Peigneux et al., 2001).

Neurobehavioral manifestations

Behavioural disturbances are common in children with SRODB with higher prevalence rates of both internalised (e.g. withdrawn, shy, anxious and psychosomatisation) and externalised (e.g. impulsivity, hyperactivity, aggression and delinquency) problematic behaviours (Blunden et al., 2001). The most frequently documented problematic behaviour in children with SROBD is inattention hyperactivity with a prevalence rate of 20-40% (Weissbluth et al., 1983; Ali et al., 1993). Conversely, children with inattention-hyperactivity showed a high prevalence rate of snoring (Chervin et al., 1997) and a co-

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diagnosis of attention-deficit hyperactivity disorder (ADHD) has been reported in 8-12% of children with OSAS (O' Brien and Gozal, 2002).

Few studies have documented that children with sleep disorders tend to have behavioral problems similar to those observed in children with attention deficit hyperactivity disorder. A survey of 782 children documented daytime sleepiness, hyperactivity, and aggressive behavior in children who snored, with 27 and 38% of children at high risk for a sleep or breathing disorder displaying clinically significant levels of inattention and hyperactive behavior, respectively (Ali et al., 1994).

Mental health

There is a lack of data about the long term effect of disturbed sleep on mental health in children.

A recent longitudinal study on the outcomes of early life sleep problems and the relation to behavior problems in early childhood stressed the importance of studying the natural history of sleep problems and their consequences to identify whether persistent or recurrent sleep problems at age 3 to 4 years are associated with comorbidities such as child behavior problems, maternal depression, and poor family functioning (Peiyoong et al., 2003).

The authors found that night waking at 3 to 4 years of age continued to be common. Seventy eight percent of mothers reported that their child awoke overnight at least once during the week, and of these waking children, 43% were reported to have awakenings 4 or more nights per week. Children with early sleep problems had significantly higher mean scores on Internalizing and Externalizing Behavior and the Aggressive Behavior and Somatic Problems subscales of the Child Behavior Checklist (CBCL).

Despite the importance of the restorative effects of sleep, there is poor information available on sleep behaviors and sleep disturbances among children and adolescents and the implications of these disturbances and problems for health. Available evidence documents those youths with disturbed sleep also experience a range of deficits in psychological, somatic, and interpersonal functioning. It has been noted that within groups of children and adolescents with psychiatric, behavioral, or emotional problems, rates of sleep disorders are elevated (Sadeh et al., 1995).

On the other hand, children and adolescents with disturbed sleep report more depression, anxiety, irritability, fearfulness, anger, tenseness, emotional instability, inattention and conduct problems, drug use, and alcohol use.

Only few longitudinal studies in adolescents evaluated the impact of insomnia on future functioning. In a large sample of 11-17 years old adolescents, followed for 1 year, using symptoms of DSM-IV criteria for insomnia, Roberts et al, (2002) found that nearly 18% of the youths 11-17 years of age report non restorative sleep almost every day in the past month, over 6% report difficulty in initiating sleep, over 5% waking up frequently during the night, another 3% had early-morning awakening almost every day, over 7% report daytime fatigue and 5% daytime sleepiness. Combining ''often'' and ''almost every day'' response categories dramatically increases prevalence, ranging from 60% for non restorative sleep to 23% for daytime fatigue and to 12% for waking up at night with difficulty to go back to sleep. The re-evaluation of sample at follow-up showed that insomnia predicted two indicators of psychological functioning: self-esteem and symptoms of depression (Roberts et al, 2002).

Growth impairment

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Failure to thrive is a well known complication of disturbed sleep and childhood OSAS. The cause of poor growth is not known, although many different reasons have been implicated: a) poor caloric intake associated with adenotonsillar hypertrophy; b) excessive caloric expenditure secondary to increased work of breathing; c) abnormal growth hormone release secondary to loss of deep non-REM sleep. The relative roles of these factors are unclear (ATS, 1999, Marcus et al., 1994). Circulating concentrations of insulin-like growth factor-I (IGF-I) and IGF-binding protein 3 (IGFBP-3), reflect mean daily GH levels, and seem to correlate well with physiologic changes in GH secretion. In the operated children with initial OSAS a highly significant reduction in Apnea-Hypopnea Index (AHI) was found and both the IGF-I and the IGFBP-3 concentrations increased significantly. GH is released in a pulsatile fashion; the initial secretion is synchronized with the onset of slow-wave sleep (SWS) and strongly correlated with slow-wave activity, within 90 to 120 minutes from the onset of sleep (Nieminen et al., 2002). In OSAS children, the sleep architecture is relatively well-preserved, but the microstructural alteration of slow-wave sleep due to microarousals induced by respiratory disturbance could play a role in the abnormal profile of GH secretion.

Cardiovascular complications

Children with OSAS had a significantly higher diastolic blood pressure (BP) than those with primary snoring. Multiple linear regression showed that blood pressure could be predicted by apnea index, body mass index, and age. The etiology of OSAS-related hypertension it is thought to be due to a number of factors, particularly sympathetic nervous system activation secondary to arousal, and to a lesser degree, hypoxemia. Although cortical arousals at the termination of obstructive apneas are less common in children than adults, children may manifest signs of subcortical arousal, including autonomic changes such as tachycardia. It is therefore possible that these subcortical arousals are associated with elevations of BP. A correlation between the frequency of obstructive apnea and BP, but no correlation between SaO2 and BP was found, suggesting that respiratory-related subcortical arousals rather than hypoxemia may be a major determinant of BP elevation in children (Marcus et al., 1998). Similarly to BP variations induced by OSAS, other studies suggest that chronic exposure to environmental noise during sleep could contribute to permanent increases in BP in otherwise healthy individuals and that no habituation to noise was apparent over three consecutive sleep sessions (Carter et al., 2002)

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VI. Identification of the possible sleep indicators of negative health effects

Most of the studies of negative effects of noise on cognitive-behavioral functioning focused on the impact of daytime noise during school hours and not on the noise in the home environment or on the noise level during nighttime.

Since, as demonstrated by the several studies presented in the previous section, the majority of negative behavioral and cognitive daytime consequences are related to sleep fragmentation as measured by arousal analysis, one of the most important future issues is to protect environment from noise, not only during daytime, but during night time.

Which are the indicators of disrupted sleep?

Indicators such as behavioral awakenings evaluated by actigraphs or sleep architecture abnormalities are not sufficient and could be misleading. A large study of the effects of aircraft noise was carried out in individuals' homes as opposed to the laboratory. The investigation showed relatively few awakenings, as measured by actigraphy, from aircraft flyovers at outdoor maximum sound levels as high as 80 dBA. The Authors concluded that the impact of aircraft noise on sleep has been overestimated (Horne J et al., 1994; Ollerhead JB, 1994). Other researchers objected to the British study's conclusions stating that it is insufficient to measure only awakening without taking into account shifts of sleep stage, which occur at much lower sound levels. In this direction, Ohrstrom found effects on subjective sleep quality and tiredness without a significant increase in awakenings (Ohrstrom E, 2002).

Further, it is well known that habituation exists for awakenings whereas other effects such as heart rate reactions and minor EEG-reactions do not habituate, as reported by Thiessen's (1978) and Ohrstrom (1988) that showed that habituation occurs for awakenings but not for sleep stage shifts and perceived sleep quality.

Potential indicators of sleep disturbance in adults are time to fall asleep, premature awakening, perceived sleep quality, daytime sleepiness and reduced performances (Ohrstrom E, 2000). However, it is known that arousal threshold is higher in children, that children are more difficult to awake, that the self perception of sleep quality is not so accurate in children and finally that sleepiness in not a typical feature of a sleep deprived children. Therefore in children, unfortunately, we can not identify sleep disruption from a behavioral point of view, based on the above mentioned indicators for adults.

We have shown in the previous sections that most of the negative health effects of disturbed sleep are mediated by the increase in arousals, meaning that microstructure of sleep is interrupted or disturbed.

For that reason, we can hypothesize that the most important sleep indicators for negative health effects are linked to the arousal system.

The analysis of arousals during sleep is important for the recovery functions of sleep and arousal density is the best predictor of daytime somnolence (Bonnet, 1985; Roehrs et al, 1989). It is known that arousability has significant implications in pediatrics: a) excessive arousability could lead to sleep disruption and insomnia potentially associated with impairment of development; b) depressed arousability is implicated in sudden infant death syndrome (SIDS) and in some forms of parasomnias.

Clinically based studies in OSAS children can elucidate this central theme. As it was reported by Marcus (2001), arousal is an important defense mechanism against sleep-disordered breathing. Apnea-related EEG arousals are less common in children than

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adults while subcortical arousals, as demonstrated by movement or autonomic changes, occur frequently.

Further, a recent study by Bandla and Gozal (2000) demonstrated that arousal identification in children based on visually identifiable EEG patterns or movement may markedly underestimate the dynamic changes in spectral EEG characteristics that were evident with obstructive episodes. Thus sleep disruption in children with OSAS is probably more subtle.

Only few published studies in children reported a significant relationship between arousal indices and neurocognitive function utilizing objective measurements (Rhodes et al., 1995, Tauman et al., 2004).

How arousals are defined in the sleep literature?

The first definition of arousals was made by the American Sleep Disorders Association in 1992:

a) an abrupt shift in EEG frequency, lasting 3 sec. or more, which may include theta, alpha, or frequencies greater than 16 Hz but not spindles;

b) subjects must be asleep (10 continuous seconds or more of any stage of sleep) before an EEG arousal can be scored and at least 10 continuous seconds of intervening sleep is necessary to score a second arousal;

c) arousals are not scored only on the basis of chin muscle tone or on changes in respiration or heart rate;

d) K complexes or delta waves are not counted as arousals unless there is also the abrupt shift to higher frequencies, seen in at least one derivation;

e) arousals in NREM can occur without any increase in chin muscle tone, whereas arousals in REM can be scored only if accompanied by an increase in submental EMG.

We should consider that, in younger children, arousals induce EEG frequencies mainly in the theta band (4-7 Hz) but with increasing age frequencies shift to the alpha band (8-13 Hz). In some studies EEG frequency shifts greater than 1 s (instead of 3 s) were considered. Mograss et al. (1994) coded the arousals in OSA children (2-11 years) and showed that most arousals were less than 3 seconds and do not necessarily disrupt sleep architecture.

Definition of what constitutes arousal is critical, and criteria of detection and scoring are still controversial (Sforza et al., 2000). Scientific papers reported different ways to codify arousals or indicators of sleep fragmentation: Arousals (ASDA, 1992), microarousals (MA) and phases of transitory activation (PAT) (Schieber et al., 1971) translate a cortical arousal response. With more sophisticated methods of arousal detection, recent studies (Halasz, 1998) opened the discussion of whether synchronized EEG sleep patterns, i.e. K-complex or delta bursts, might represent a form of arousal response in humans. The authors found that stimuli-induced arousals consisted of transient EEG patterns, without subsequent EEG desynchronization and associated with autonomic activation. These events, called subcortical or autonomic arousal (Martin et al., 1997), are intrinsic components of human sleep, appearing spontaneously as phases A1 of cyclic alternating pattern (CAP) (Terzano et al., 2001) and expression of levels of greater or lesser arousal. One major subject of discussion in sleep studies is whether bursts of K-complexes (K-bursts) and delta waves (D-bursts), expressions of a subcortical arousal, truly reflect an arousal response during sleep. It is known that responses to auditory stimulation in humans induce vasoconstriction, blood pressure variations, and increase in ventilation, concomitant with bursts of K-complexes or delta waves; moreover, delta

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bursts occur in patients with upper airway resistance syndrome and OSAS as an arousal response to airflow limitation (Sforza et al., 2000).

Using heart rate (HR) variation over time Sforza et al. (2000) found a significant change in HR during K- and Delta-bursts consisting of a tachycardia followed by a bradycardia, reflecting the changes seen during MA and PAT but to a lesser degree. The link between EEG and HR variation during MA and PAT and the fluctuations in HR during subcortical arousal suggest a continuous spectrum in the arousal mechanisms, starting at the brainstem level and progressing to cortical areas. Thus, subcortical arousals might represent the primary form of arousal response in sleep, preceding the appearance of a cortical arousal and implicating a common mechanism in the human arousal response.

These so called "subcortical arousals" (K-bursts and delta bursts) are included in the events that are coded as phase A1 in CAP atlas from Terzano et al. (2001) which have also been shown to be able to modify significantly heart rate variability during sleep in children (Ferri et al. 2000).

Significance of CAP

During NREM, sleep maintains an oscillating pattern that reflects different levels of arousal that has been coded as CAP. CAP is a periodic EEG activity of NREM sleep characterized by repeated spontaneous sequences of transient events (phase A) which clearly breaks away from the background rhythm of the ongoing sleep stage, with an abrupt frequency/amplitude variation, recurring at intervals up to 1 min long. The return to background activity identifies the interval that separates the repetitive elements (phase B) (Terzano et al., 2001). CAP A phases have been subdivided into a 3-stage hierarchy of arousal strength:

– *A1*: A phase with synchronized EEG patterns (intermittent alpha rhythm in stage 1; sequences of K-complexes or delta bursts in the other NREM stages), associated with mild or trivial polygraphic variations;

– *A2*: A phase with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves (K-complexes with alpha and beta activities, k-alpha, arousals with slow wave synchronization), linked with a moderate increase of muscle tone and/or cardiorespiratory rate;

– *A3*: A phase with desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding 2/3 of the phase A length, and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate

This hierarchical activation from the slower EEG patterns (moderate autonomic activation without sleep disruption) to the faster EEG patterns (robust vegetative activation associated with visible sleep fragmentation) can have different meanings: A1 subtypes are involved in the build-up and maintenance of deep NREM sleep, can have a protective role for sleep continuity and could be related to different hormonal and physiological activities of NREM sleep; A2 and A3 can be involved in the REM-on activity and have the function of maintaining the subject arousability (Terzano and Parrino, 2000).

CAP has been related to several physiological and pathological conditions in adults (noise, insomnia, parasomnias, sleep disordered breathing, epilepsy, etc.) and can be viewed as a new paradigm to explore the pathophysiological bases of sleep disorders and to evaluate the effects of sleep stressors on sleep structure to identify the indicators of daytime consequences of sleep.

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CAP and its relationships with noise

Only two studies evaluated the effects of noise on CAP. Terzano et al. (1990) showed that with increasing intensity of sound pressure level (basal condition followed by continuous white noise at 45 dBA, 55 dBA, 65 dBA and 75 dBA), all the macrostructural components of sleep were affected, demonstrating a linear relationships with the sound pressure levels. For the microstructure of sleep, white noise induced a remarkable enhancement of CAP/NREM, characterized by a linear trend from the lowest to the highest intensities with increase of CAP rate associated with increasing disruption of REM and NREM stage 4. The greatest increase of CAP rate was detected in NREM stage 4, the duration of which underwent remarkable changes both at the lowest and the highest sound pressure levels. For CAP/NREM values between 45% and 60%, subjects generally recalled a moderate nocturnal discomfort and values of CAP/NREM over 60% corresponded to a severe complaint.

In 1993, Terzano et al. studied two groups of healthy subjects that slept in a random sequence for two non-consecutive nights either under silent baseline or noise-disturbed conditions. Total NREM sleep described by traditional parameters was statistically unaffected during the disturbed nights, but the perturbing effects of noise on NREM sleep stability and continuity were revealed by a significant increase in the CAP rate at 45 dB(A). Irrespective of the specific age, noise decreased mainly SWS, REM and total sleep time, and increased wake after sleep onset, Stage 1 NREM and the CAP rate.

The Authors concluded that under the thrust of increasing sound pressure levels, CAP operates as a "buffer" mechanism that counteracts, within compatible ranges, the disruptive effects of noise on the macrostructure of sleep. This result corroborates previous findings described by Lukas (1972, who reported that reactions less than a sleep stage change correlate better to the noise intensity than awakening reactions.

Linking CAP with arousals and behavioral-cognitive dysfunction in children

The issue of the link between CAP, arousal and behavioral-cognitive dysfunction is important in children for several reasons:

    a) arousal threshold is higher in children
    b) the more stable homeostatic process of sleep does not permit a clear macrostructural disruption
    c) stimulus-related EEG arousals are less common in children than adults while subcortical arousals, as demonstrated by movement or autonomic changes, occur frequently
    d) many obstructive respiratory events may not be terminated by an arousal thus preserving sleep architecture
    e) arousal identification in children based on visually identifiable EEG patterns or movement may markedly underestimate the dynamic changes in spectral EEG characteristics that were evident with obstructive episodes
    f) self perception of sleep quality is not so accurate in children

CAP analysis of sleep in children can give new insights on the relationships between sleep disruption and cognitive consequences. This kind of analysis can be valuable in assessing children whose daytime learning and behavior might be adversely affected by disruption of their sleep, even with apparently normal sleep macrostructure.

Few studies have been carried out on CAP in children. Bruni et al., 2002 showed that sleep of school-aged children, considered as the 'gold standard' for sleep quality, is rich of phases A1 (mainly K-bursts and delta bursts). In the build-up and maintenance of deep sleep, activation events are composed basically of subtypes A1. We can

hypothesize that, since the restorative value of sleep is related to SWS, the A1 subtypes could play an important role in maintaining this function. Phases A1 can be therefore considered as a reinforcement of sleep rather than an arousal phenomenon and protective against factors that could lead to sleep disruption. Further, A1 subtypes undergo a complex development in association with topical maturational epochs showing a peak in the pre-adolescents and adolescents, which is probably associated to specific metabolic age-related variations, especially the growth hormone secretion (Terzano et al., 2003).

Recently, Bruni et al (2003) presenting preliminary data on CAP in pre-school children and comparing with the school age group, found an increase of A2 phases. In younger children the most common pattern of EEG frequency changes associated with an arousal is a shift to a more rhythmic pattern, primarily in the theta-alpha range that was coded as A2 phases. This EEG pattern should be considered as an arousal pattern typical of this age range. The higher prevalence of A2 phases could represent a signal of higher sleep instability in this age range.

Clinical applications of this new method of scoring are beginning to be explored.
Sleep disorders such as OSA in children, can affect CAP. We analyzed CAP in 9 OSAS children and we did not find differences in macrostructural parameters and in CAP rate but a decrease in A1 phases and an increase in A2 phases, mainly during SWS (Bruni et al., 2003).

We report unpublished data that analyze the relationships between CAP and neurobehavioral functioning. We studied, in collaboration with the Centre for Sleep Research, Dept. of Paediatrics, University of Adelaide, South Australia, 17 children (6 M, 11 F; mean age 7,6 years) that underwent standard polysomnography and neuropsychological evaluation including: Wechsler Intelligence Scale for Children (WISC-III); Wide Range Assessment of Memory and Learning (WRAML); Auditory Continuous Performance test (ACPT); Child Behavior Checklist (CBCL). Statistical analysis showed positive correlation between WISC-III performance IQ and total A1 percentage (r .84) and A1 duration (r .59), while negative correlation has been found with A2 percentage (r -.78). CBCL Internalizing score negatively correlated with A2-A3. WISC III verbal IQ, WRAML and ACPT did not show a relationship with CAP parameters.

The visual analysis of CAP allows to recognize 2 main frequency components belonging, respectively, to the low delta range (phase A1) and to the alpha-beta range (phase A2 and A3).
The quantitative spectral analysis of these different A phase subtypes, by means of the FFT, showed that the low-frequency band (0.25-2.5 Hz) had a clear prevalence over the anterior prefrontal-frontal regions, while the high-frequency band (7-15 Hz) involved mostly the parietal-occipital areas. The analysis of the cortical generators of the two frequency bands of CAP, carried out by means of the "low resolution brain electromagnetic tomography", confirmed that the generators of the low-frequency component of CAP are localized mostly over the frontal midline cortex and those of the high-frequency band involve the parietal and occipital areas (Ferri et al., 2004).
The low frequency components (A1) are mostly represented during SWS and SWS is now widely recognized as involved in different functions (cognition, behavior, growth hormone secretion, ecc.); we can hypothesize that SWS disruption induced by

respiratory disturbances or noise or other factors can be responsible of daytime consequences of sleep fragmentation.

Considering that:

a) a positive correlation exists between performance IQ and A1 phases;
b) A1 in children are mostly represented during SWS (Bruni et al., 2002);
c) in OSAS children the decrease of A1 phases and the corresponding increase of A2 was mainly observed in SWS (Bruni et al., 2003);
d) A1 phases generators are located in the prefrontal-frontal cortex;
e) the prefrontal cortex is involved in executive cognitive functions;
f) negative cognitive effects are mediated by prefrontal cortex dysfunction induced by OSA;
g) the factor responsible for the daytime effects in OSAS children is sleep fragmentation other than hypoxemia;

we can hypothesize that the disruption of sleep continuity and mainly the fragmentation of SWS, with a reduction of A1 (generated in prefrontal cortex) and an increase of A2, could alter the homeostatic process that is necessary for prefrontal cortex restoration and for 'recalibration' of prefrontal cortex circuits and lead to cognitive dysfunctions .

Other new indicators of sleep disruption

These new scoring parameters can allowed us to evaluate the effects of different factors affecting sleep and therefore specify the exact indicators of negative health effects.

Following this direction, new markers of sleep disruption are currently being developed. In an in press paper, Tauman et al. (2004) identified a new parameter of sleep disruption named Sleep Pressure Score (SPS). It is derived from a calculation between indexes of all arousals during sleep (ARtotI), of spontaneous arousals (SAI) and of respiratory related arousals (RAI): *SPS = (RAI/ARtotI) x (1-SAI/ ARtotI).* This new parameter has been correlated with cognitive measures and it has been found that SPSHigh children were significantly more likely to have deficits in memory, language abilities, verbal abilities, and some visuospatial functions than children with SPSLow, that are consistent with prefrontal cortex (PFC) dysfunction, in agreement with the Beebe and Gozal model (2002). Thus, a simple quantitative measure of sleep perturbation derived from the polysomnographic distribution of respiratory and spontaneous arousals provides a sensitive correlate of cognitive function in snoring children and demonstrated that sleep fragmentation imposes adverse effects on daytime pre-frontal cortical performance in children that is independent of the effects of episodic hypoxia and hypercapnia.

VII. Conclusions

Reviewing our entire dissertation, we have sufficient evidences that disturbance of the arousal system and sleep fragmentation, either evaluated as cortical or subcortical arousals, CAP or SPS, are implicated in determining all medium and long term negative consequences.

Due to the paucity of studies on this argument we propose a shortlist of future research priorities:

- Analysis of sleep microstructure in normal children
- Analysis of sleep microstructure in learning disabled children
- Analysis of sleep microstructure in behaviorally disturbed children
- Correlation between alteration of sleep microstructure and behavioral and cognitive functioning in children
- Prevention of negative cognitive consequences of disturbed sleep
- Identification of possible therapies to avoid sleep disruption (behavioral techniques, drugs, etc.)
- Sensibilization of pediatricians and physicians about the importance of sleep for development

VIII. References

1. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. Eur J Pediatr 1996; 155: 56-62

2. Ali NJ, Pitson D, Stradling JR. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. Arch Dis Child 1994; 71:74-76

3. ASDA (American Sleep Disorders Association). EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992; 15: 174-184

4. ATS - American Thoracic Society. Cardiorespiratory Sleep Studies in Children. Establishment of Normative Data and Polysomnographic Predictors of Morbidity. Am J Respir Crit Care Med 1999; 160: 1381-1387

5. Bandla HP, Gozal D. Dynamic chnages to EEG spectra during obstructive apnea in children. Pediatr Pulm 2000; 29: 359-365

6. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002; 11:1-16

7. Berglund B, Lindvall TH, Schwela DH, eds. Guidelines for community noise. World Health Organization: Geneva 2000; http://www.who.int./peh/noise/noiseindex.html

8. Bistrup ML, ed. Health effects of noise on children and the perception of the risk of noise. Copenhagen, National Institute of Public Health. 2001

9. Bistrup ML. Prevention of Adverse Effects of Noise on Children. Noise Health 2003; 5:59-64

10. Blunden S, Lushington K, Kennedy D. Cognitive and behavioural performance in children with sleep-related obstructive breathing disorders. Sleep Med Rev 2001; 5: 447-461

11. Blunden SL, Lushington K, Kennedy D, Martin J, Dawson D. Behaviour and Neurocognitive Function in Children aged 5-10 years who snore compared to Controls. J Clin Exp Neuropsychol 2000; 22: 554- 568

12. Bonnet MH. Effect of sleep disruption on sleep, performance, and mood. Sleep 1985; 8:11-19

13. Bruni O, Ferri R, Miano S, Verrillo E, Vittori E, Della Marca G, Farina B, Mennuni G. Sleep cyclic alternating pattern in normal school-age children. Clin Neurophysiol 2002; 113: 1806-1814

14. Bruni O, Ferri R, Villa MP, Miano S, Verrillo E, Ambrosio R, Terzano MG. Cyclic Alternating Pattern in Obstructive Sleep Apnea Children. Sleep, 26: A131-132, 2003

15. Bruni O, Miano S, Ferri R, Smerieri A, Parrino L, Verrillo E, Farina B, Terzano MG. Cyclic alternating pattern in normal preschool‐age children. Abstract Book 13th Meeting of the European Pediatric Sleep Club, Rome, November 22-23, 2003; pp. 9-10

16. Busby K, Pivik RK. Auditory arousal threshold during sleep in hyperkinetic children. Sleep 1985; 8: 332-341

149

17. Carter N, Henderson R, Lal S, Hart M, , Booth S, Hunyor S. Cardiovascular and Autonomic Response to Environmental Noise During Sleep in Night Shift Workers. Sleep 2002; 25: 444-451

18. Chervin RD, Dillon JE, Bassetti C, Ganoczy DA, Pituch KJ. Symptoms of Sleep Disorders, Inattention, and Hyperactivity in Children. Sleep 1997; 20: 1185-1192

19. Dahl RE. The impact of inadequate sleep on children's daytime and cognitive function. Seminars Pediatric Neurol 1996; 3: 44- 50

20. Di Nisi J, Muzet A, Ehrhart J, Libert JP. Comparison of cardiovascular responses to noise during waking and sleeping in humans. Sleep 1990; 13:108-120

21. Eberhardt JE. The disturbance by road traffic noise of the sleep of prepubertal children as studied in the home. In: Berglund B, Lindvall T, ed. Noise as a public health problem. Stockholm: Swedish Council for Building Research 1988

22. Ehrhart J, Muzet A. Frequence et duree des phases d'activation transitoire au cours du sommeil normal ou perturbé chez l'homme. Arch Sci Physiol 1974 ; 28: 213-260

23. Feinberg I, Thode HC, Chugani HT, March JD. Gamma function describes maturational curves for delta wave amplitude, cortical metabolic rate and synaptic density. J Theor Biol 1990; 142: 149-161

24. Ferri R, Parrino L, Smerieri A, Terzano MG, Elia M, Musumeci SA, Pettinato S. Cyclic alternating pattern and spectral analysis of heart rate variability during normal sleep. J Sleep Res 2000 Mar;9(1):13-18.

25. Ferri R, Bruni O, Miano S, Terzano MG. Scalp Topography and Cortical Generators of the Spectral Components of the "Cyclic Alternating Pattern" (CAP). Handbook of Neurophysiology. Sleep Disorders, C. Guilleminault Ed. Elsevier (In press)

26. Giannotti F, Cortesi F, LeBourgeois MK, Sebastiani T, Vagnoni C, Carta F. Sleep hygiene in italian preschoolers and school-aged children. Sleep supplement 2004; in press,

27. Gozal D, Pope DW. Snoring During Early Childhood and Academic Performance at Ages Thirteen to Fourteen Years. Pediatrics 2001; 107: 1394-1399

28. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998; 102: 616- 620

29. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998; 102:616-620

30. Guilleminault C, Pelayo R, Leger D, Clerk A, Bocian RCZ. Recognition of Sleep Disordered Breathing in Children. Pediatrics 1996; 98: 871-882

31. Guilleminault C, Winkle R, Korobkin R, Simmons B. Children and nocturnal snoring: Evaluation of the effects of sleep related respiratory resistive load and daytime functioning. Eur J Pediatr 1982; 139: 165-171

32. Haines MM, Brentnall SL, Stansfeld SA, Klineberg E. Qualitative responses of children to environmental noise. Noise Health 2003; 5:19-30

33. Haines MM, Stansfeld SA, Brentnall S, Head J, Berry B, Jiggins M, Hygge S. The West London Schools Study: the effects of chronic aircraft noise exposure on child health. Psychol Med 2001; 31:1385-1396

34. Halasz P. Hierarchy of micro-arousals and the microstucture of sleep. Neurophysiol Clin 1998; 28: 461-475

35. Harrison Y, Horne JA, Rothwell AL. Prefrontal neuro-psychological effects of sleep deprivation in young adults - A model for healthy aging? Sleep 2000; 23: 1067-1073

36. Hobson JA, Pace-Schott EF. The Cognitive Neuroscience of Sleep: Neuronal Systems, Consciousness and Learning. Nature Rev Neurosc 2002; 3: 679-693

37. Horne JA, Pankhurst FL, Reyner LA, Hume K, Diamond ID. A field study of sleep disturbance: effects of aircraft noise and other factors on 5,742 nights of actimetrically monitored sleep in a large subject sample. Sleep 1994; 17(2):146-59

38. Lercher P, Evans GW, Meis M, Kofler WW. Ambient neighbourhood noise and children's mental health. Occup Environ Med 2002; 59:380-386

39. Lewin DS, England SJ, Rosen RC. Cognitive and behavioural sequelae of obstructive sleep apnea in children. Sleep 1999; 22: S126

40. Lukas JS. Effects of aircraft noise on human sleep. Am Ind Hyg Assoc J 1972; 33: 298-303

41. Macey PM, Henderson LA, Macey KE, Alger JR, Frysinger RC, Woo MA, Harper RK, Yan-Go FL, Harper RM. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002; 15;166:1382-1387

42. Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre C, Meulemans T, Luxen A, Franck G, Van Der Linden M, Smith C, Cleeremans A. Experience-dependent changes in cerebral activation during human REM sleep. Nature Neurosci 2000; 3:831-836

43. Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 2000; 9:207-231

44. Marcus CL, Carroll JL, Koerner CB, Hamer A, Lutz J, Loughlin GM. Determinants of growth in children with the obstructive sleep apnea syndrome. J Pediatr 1994;125:556-562

45. Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998; 157:1098-1103

46. Marcus CL. Sleep-disordered Breathing in Children. Am J Respir Crit Care Med 2001; 164: 16-30

47. Martin SE, Wraith PK, Deary U, Douglas NJ. The effect of non-invisible sleep fragmentation on daytime function. Am J Respir Crit Care Med 1997; 155:1596-1601

48. Mcdonald DG, Schicht WW, Frazier RE, Schallenberger HD and Edwards DJ. Studies of information processing in sleep. Psychophysiology 1975; 12:624-629

151

49. Mograss MA, Ducharme FM, Brouilette RT. Movement/ Arousal. Description, classification, and relationship to sleep apnea in children. Am J Respir Crit Care Med 1994; 150:1690-1696

50. Muzet, A, Naitoh P. Sommeil et bruit. Confront Psychiat 1977; Suppl. 1:215-235

51. Nieminen P, Lopponen T, Tolonen U, Lanning P, Knip M, Lopponen H. Growth and Biochemical Markers of Growth in Children With Snoring and Obstructive Sleep Apnea. Pediatrics 2002; 109: e55

52. O'Brien LM, Gozal D. Behavioral and neurocognitive implications of snoring and obstructive sleep apnea in children: facts and theory. Pediatric Resp Rev 2002; 3:3-9

53. Ohrstrom E, Bjorkman M. Effects of noise-disturbed sleep - a laboratory study on habituation and subjective noise sensitivity. J Sound Vib 1988; 122:277-290

54. Ohrstrom E. Sleep disturbances caused by road traffic noise - studies in laboratory and field. Noise Health 2000; 8: 71-78

55. Ohrstrom E. Sleep Studies Before and After - Results and Comparison of Different Methods. Noise Health 2002; 4:65-67

56. Ollerhead JB. Report of a Field Study of Aircraft Noise and Sleep Disturbance: A Study Commissioned by three Department of Transport from the Civil Aviation Authority, HMSO 1994.

57. Oswald J, Taylor AM, Treisman M. Discriminative responses to stimulation during human sleep. Brain 1960; 83,440-453

58. Owens-Stively J, McGuinn M, Berkelhammer L, Marcotte A, Nobile C, Spirito A. Neuropsychological and behavioral correlates of obstructive sleep apnea in children. Sleep Res 1997; 26 (Suppl 1): 452

59. Passchier-Vermeer W. Effects of noise. In: Health effects of noise on children and perception of the risk of noise. Bistrup ML Ed. 2001, pp. 47-68

60. Peigneux P, Laureys S, Delbeuck X, Maquet P. Sleeping brain, learning brain. The role of sleep for memory systems. NeuroReport 2001; 12:A111-A124

61. Peiyoong L, Hiscock H, Wake M. Outcomes of Infant Sleep Problems: A Longitudinal Study of Sleep, Behavior, and Maternal Well-Being. Pediatrics 2003; 111: 203-207

62. Rechtschaffen A, Hauri P, Zeitlin M. Auditory awakening thresholds in REM and NREM sleep stages. Percept Motor Skills 1966; 22: 927-942

63. Rhodes SK, Shimoda KC, Waid LR, O'Neil PM, Oexmann MJ, Collop NA, Willi SM. Neurocognitive deficits in morbidly obese children with obstructive sleep apnea. J Pediatr 1995; 127: 741-744

64. Richards W, Ferdman RM. Prolonged morbidity due to delays in the diagnosis and treatment of obstructive sleep apnea in children. Clin Pediatr 2000; 39: 103-108

65. Robert E, Roberts CR, Chen IG. Impact of insomnia on future functioning of adolescents. J Psychosom Res 2002; 53: 561- 569

66. Sadeh A, McGuire JP, Sachs H, Seifer R, Tremblay A, Civita R, Hayden RM.Sleep and psychological characteristics of children on a psychiatric inpatient unit. J Am Acad Child Adolesc Psychiatry. 1995; 34(6):813-819

67. Sadeh A, Gruber R, Raviv A.Sleep, neurobehavioral functioning, and behavior problems in school-age children. Child Dev. 2002; 73(2):405-417.

68. Sadeh A, Gruber R, Raviv A.The effects of sleep restriction and extension on school-age children: what a difference an hour makes. Child Dev. 2003; 74(2):444-455

69. Schieber JP, Muzet A, Ferriere PJR. Les phases d'activation transitoire spontanées au cours du sommeil normal chez l'homme. Arch Sci Physiol 1971; 25: 443-465

70. Sejnowski TJ, Destexhe A. Why do we sleep? Brain Research 2000; 886: 208-223

71. Sforza E, Jouny C, Ibanez V. Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response. Clin Neurophysiol 2000; 111:1611-1619

72. Smeczuk B. Studies on the influence of acoustic stimuli on respiratory movements. Pol Med J 1967; 7: 1090-1100

73. Steenari MR, Vuontela V, Paavonen EJ, Carlson S, Fjällberg M, Aronen ET. Working Memory and Sleep in 6- to 13-Year-Old Schoolchildren. J Am Acad Child Adolesc Psychiatry 2003; 42:85-92

74. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: a multi-step process occurring during sleep. J Cogn Neurosci 2000; 12: 246-254

75. Stradling JR, Thomas G, Warley ARH, Williams Freeland A. Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance and symptoms in snoring children. Lancet 1990; 335: 249-253

76. Terzano M G, Parrino L, Fioriti G, Orofiamma B, Depoortere H. Modifications of sleep structure induced by increasing levels of acoustic perturbation in normal subjects. EEG Clin Neurophys 1990; 76: 29-38

77. Terzano MG, Parrino L, Spaggiari MC, Buccino GP, Fioriti G, Depoortere H. Assessment of Noise-Induced Sleep Fragility in Two Age Ranges by Means of Polysomnographic Microstructure. J Sound Vib 1993; 162:345-359

78. Terzano MG, Parrino L, Smerieri A, Bruni O, Miano S, Ferri R, Verrillo E. Cyclic alternating pattern (CAP) during life‐span. Abstract Book 13th Meeting of the European Pediatric Sleep Club, Rome November 22-23, 2003; pp. 7-8

79. Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, Hirshkowitz M, Mahowald M, Moldofsky H, Rosa A, Thomas R, Walters A. Consensus Report. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 2001; 2:537-553

80. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev 2000;4:101-123

81. Thiessen G. Disturbance of sleep by noise. JASA 1978; 64:216-222

153

82. Vallet M, Mouret J. Sleep disturbance due to transportation noise: ear plugs vs oral drugs. Experientia 1984; 40: 429-437

83. Weissbluth M, Davis AT, Poncher J, Reiff J. Signs of airway obstruction during sleep and behavioral, developmental and academic problems. J Dev Behav Pediatr 1983; 4:119-121

ABBREVIATIONS

ACPT=Auditory Continuous Performance Test;
ADHD=Attention Deficit Hyperactivity Disorder;
ADHD=Attention Deficit Hyperactivity Disorder;
AHI=Apnea/Hypopnea Index;
ARtotI=Total arousals Index:
BP=Blood Pressure;
CAP=Cyclic Alternating Pattern;
CBCL=Child Behaviour Checklist;
FFT=Fast Fourier Transform;
HR=heart rate;
IQ=Intelligence Quotient;
MA=Microarousals;
NREM= Non Rapid Eye Movement;
OSAS=Obstructive Sleep Apnea Syndrome;
PAT= Phases of Transitory Activation;
PFC=Prefrontal Cortex;
RAI=Respiratory-related Arousals Index;
REM=Rapid Eye Movement;
SAI=Spontaneous Arousals Index;
SPS=Sleep Pressure Score;
SROBD=Sleep-Related Obstructive Breathing Disorders;
SWS=Slow Wave Sleep;
UARS=Upper Airway Resistance Syndrome;
WISC-III=Wechsler Intelligence Scale for Children 3rd edition;
WRAML=Wide Range Assessment of Memory and Learning.

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Sleep - gender, age, stress, work hours, Torbjörn Åkerstedt

IPM/Karolinska institute, Box 230 , 17177 Stockholm Sweden
Phone: 46 8 7286945, fax: 46 8 320521, e-mail: torbjorn.akerstedt@ipm.ki.se

Executive summary

The present review suggests that the risk of disturbed sleep increases with age but there also seems to be a recent stress related increase in sleep disturbances in young adults. The long term health consequences are not understood.

The relation between gender and disturbed sleep is confusing. Females, as a rule complain more of sleep problems, but do not exhibit any objective indications of more disturbed sleep at least not among otherwise healthy women. With increasing age the sleep of males deteriorate whereas that of women is relatively well upheld. Pregnancy, however, is a period of increased risk of disturbed sleep , whereas the menstrual cycle and menopause show less evidence of disturbed sleep. Clearly there is a great need of longitudinal research on gender and sleep and in particular on the possible health consequences around pregnancy.

Stress due to work or family seems to be one of the major causes of disturbed sleep. The effects on the risk of insomnia is well established, but reduced sleep in itself seems to yield the same physiological changes as stress. This suggests that several of the major civilization diseases in Europe and the US (diabetes, cardiovascular disease, burnout) could be mediated via disturbed sleep. This link clearly warrants longitudinal studies with interventions.

Shift workers constitute a group that suffers from disturbed sleep for most of their occupational life. The reason is the interference of work hours with the normal timing of sleep. This leads to an increased risk of accidents, directly due to excessive sleepiness, but also to cardiovascular and gastrointestinal disease, although it is not clear whether the latter effects are sleep related or due to circadian factors - or to a combination. Recent studies also suggest that breast cancer may result from shift work due to the effects of light on melatonin secretion. This still needs verification, however. Future research needs to identify countermeasures, the reasons for large individual differences in tolerance and the possible cancerogenic and other effects.

The conclusions above should be seen against the profound effects of reduced or fragmented sleep on the neuroendocrine (including glucose and lipid regulation) and immune systems as well as the effects on mortality, diabetes and cardiovascular disease.

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Introduction

The present paper is focused on the basic individual factors and two risk groups that clearly run the risk of disturbed sleep in normal daily life. The two obvious individual factors in this context is age and gender. The two risk groups are those exposed to stress and those who have their work hours interfere with normal sleep hours.

Gender & age

Gender turns up an important predictor of disturbed sleep in virually all epidemiological studies. (Bixler et al., 1979; Karacan et al., 1976, Ancoli-Israel, 1999 #4652; Sateia et al., 2000; Leger et al., 2000). On the other hand there doesn't seem to be much of a difference in polysomnographical parameters between males and females, except for the former loosing SWS with increasing age and having a slightly reduced sleep efficiency also with increasing age (Williams et al., 1974) (Hume et al., 1998). Ehlers et al timed the start of differences between genders to 20-40 years (Ehlers and Kupfer, 1997). Also spectral analysis indicates slightly larger amounts of low frequency activity in females (Dijk et al., 1989a; Dijk et al., 1989b). In addition, men seem to run a higher risk for morbidity and mortality related to sleep problems than women (Nilsson et al., 2001). The inconsistency between polysomngraphy and subjective measures has not bee resolved but it may be important that most polysomnographical studies have control for anxiety and depression. Thus, it is conceivable that the higher level of subjective complaints in women reflects a higher prevalence of anxiety. The latter is a speculation, however.

A confounding factor in gender comparisons is that also phase in female biological cycles is usually controlled for in polysomnographical studies, meaning that potential effects of, for example, menstruation, may not receive its proper weight. A recent review has gone through the literature i this area (Moline et al., 2003). It found that the luteal phase of the menstrual cycle is associated with subjective sleep problems, but this has not been supported by polysomnographical studies. Pregnancy affects sleep negatively already in the first trimester and the effects mainly involve awakenings and difficulties getting back to sleep. Napping is a frequent coping method. The post-partum period is often associated with severe sleep disruption, mainly due to feeding and comforting the infant. There seems to be some relation between sleep disruption and post-partum mood, but nothing is known about the causal relations. Menopause seems to involve disrupted sleep in relation to hot flashes, depression/anxiety and sleep disordered breathing. Estrogen is associated with improved sleep quality but it is not clear whether the effects is via a reduction of hot flashes. Estrogen also improves sleep-disordered breathing.

With respect to background factors, age is an established predictor of disturbed sleep (Bixler et al., 1979; Karacan et al., 1976; Ancoli-Israel and Roth, 1999; Ribet and Derriennic, 1999; Sateia et al., 2000; Leger et al., 2000). Interestingly, though, older age may be related to a *lower* risk of impaired awakening (Åkerstedt et al., 2002c), that is, in this study it was easier to wake up and one felt more well rested with increasing age, while at the same time, sleep quality was lower. The increased risk of disturbed sleep is consistent with the increasingly strong interference of the circadian morning upswing of metabolism with increasing age (Dijk and Duffy, 1999). Thus sleep maintenance is impaired and when sleep is interrupted "spontaneously", the awakening is, by definition, easily accomplished and will be lacking in inertia. This ease of awakening may be

interpreted as "being well rested", and obviously the need for sleep is not great enough to prevent an effortless transition into wakefulness.

In addition, sleep homeostasis seems to be weakened with age in the sense that sleep becomes more fragmented and SWS or power density in the delta bands decreases (Williams et al., 1974) (Bliwise, 1993; Dijk et al., 1999). As mentioned above, the effects are more pronounced in males, a fact may be linked to reduced levels of growth hormone and testosterone.

Stress

A number of epidemiological studies point to a strong link between stress and sleep (Åkerstedt, 1987; Ancoli-Israel and Roth, 1999; Urponen et al., 1988). In fact, stress is considered the primary cause of persistent psychophysiological insomnia (Morin et al., 2003). Also, recent epidemiological studies have shown a connection between disturbed sleep and later occurrence of stress-related disorders such as cardiovascular disease (Parish and Shepard, 1990; Nilsson et al., 2001; Leineweber et al., 2003) and diabetes type II (Nilsson et al., 2002). The mechanism has not been identified but both lipid as well as glucose metabolism is impaired in relation to experimentally reduced sleep (Åkerstedt and Nilsson, 2003).

Burnout is another result of long term stress and a growing health problem in many western countries (Weber and Jaekel-Reinhard, 2000). In Sweden, burnout is estimated to account for most of the doubling of long-term sickness absence since the mid-nineties (RFV, 2003). The characteristic clinical symptoms of the condition are excessive and persistent fatigue, emotional distress and cognitive dysfunction (Melamed et al., 1992; Kushnir and Melamed, 1992). Self-reports of disturbed sleep are pronounced in subjects scoring high on burnout (Melamed et al., 1999; Grossi et al., In press). Since shortened and fragmented sleep is related to daytime sleepiness and impaired cognitive performance (Bonnet, 1986b; Bonnet, 1986a; Bonnet, 1985; Dinges et al., 1997; Gillberg and Åkerstedt, 1998; Åkerstedt, 1990), disturbed sleep might provide an important link between the state of chronic stress and the complaints of fatigue and cognitive dysfunction seen in burnout.

Partinen et al (1984) investigated several occupational groups and found disturbed sleep to be most common among manual workers and much less so among physicians or managing directors. Geroldi et al (1996) found in a retrospective study of older individuals (above the age of 75) that former white collar workers reported better sleep than blue collar workers. Kupperman et al (1995) reported less sleep problems in subjects satisfied with work.

In what seems to be the most detailed study so far, Ribet et al (1999) studied more than 21000 subjects in France, using a sleep disturbance index and logistic regression analysis. It was found that shift work, a long working week, exposure to vibrations, and "having to hurry" appeared to be the main risk factors, controlling for age and gender. Disturbed sleep was (Bixler et al., 1979; Karacan et al., 1976; Ancoli-Israel and Roth, 1999), more frequent in women, and in higher age groups.

The particular stressor linked to disturbed sleep may be working under high demands. (Urponen et al., 1988; Ancoli-Israel and Roth, 1999; Ribet and Derriennic, 1999; Åkerstedt et al., 2002b)]. High demands is the classical work stress factor and when combined with low decision latitude it has been shown to be related to cardiovascular disease (Theorell et al., 1998) and absenteeism (North et al., 1996). Interestingly, when "persistent thoughts about work" was added to the regression in the study by Akerstedt

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et al (2002b) this variable took over part of the role of work demands as a predictor. This suggests that it may not be work demands *per se* that are important, but rather their effect on post-work unwinding. In two studies it has been demonstrated that even moderate worries about being awakened during the night or of having a negative feeling about the next day will affects sleep negatively, mainly reducing SWS (Torsvall and Åkerstedt, 1988; Kecklund and Åkerstedt, 1997). On the other hand there is very little data to connect real life stress with polysomnograhical indicators of disturbed sleep. Most studies have used rather innocuous and artificial stressor in a lab environment. Field studies of stress are virtually lacking, with some exceptions (Hall et al., 2000).

Also lack of social support at work is a risk indicator for disturbed sleep (Åkerstedt et al., 2002b). We have not been able to find much previous data of this type but poor (general) social support has been associated with sleep complaints in Vietnams veterans (Fabsitz et al., 1997). On the other hand, there are a number of studies indicating a close connection with poor social support for, for example, cardiovascular disease (Arnetz et al., 1986), or muscle pain (Ahlberg-Hultén et al., 1995).

Interestingly, the metabolic changes seen after sleep curtailment in normals or in insomniacs and sleep apneics are similar to those seen in connection with stress. That is, lipid and glucose metabolism are increased, as are cortisol levels (Spiegel et al., 1999; Vgontzas et al., 2001; Vgontzas et al., 2000). Together with the prospective links to stress related diseases such as diabetes type II and cardiovascular disease discussed above, and with mortality (Kripke et al., 1979; Kripke et al., 2002; Åkerstedt et al., 2002a; Dew et al., 2003), the findings could suggest that disturbed sleep may be an important mediator in the development of stress-related diseases.

Shift work

The dominating health problem reported by shift workers is disturbed sleep and wakefulness. At least 3/4 of the shift working population is affected. (Åkerstedt, 1988). When comparing individuals with a very negative attitude to shift work with those with a very positive one, the strongest discriminator seems to be the ability to obtain sufficient quality of sleep during daytime (Axelsson et al., submitted). EEG studies of in rotating shift workers and similar groups have shown that day sleep is 1-4 hours shorter than night sleep (Foret and Lantin, 1972; Foret and Benoit, 1974; Matsumoto, 1978; Tilley et al., 1981; Torsvall et al., 1989; Mitler et al., 1997). The shortening is due to the fact that sleep is terminated after only 4-6 hours without the individual being able to return to sleep. The sleep loss in is primarily taken out of stage 2 sleep ("basic" sleep) and stage REM sleep (dream sleep). Stages 3 and 4 ("deep" sleep) do not seem to be affected. Furthermore, the time taken to fall asleep (sleep latency) is usually shorter. Also night sleep before a morning shift is reduced but the termination is through artificial means and the awakening usually difficult and unpleasant. (Dahlgren, 1981a; Tilley et al., 1982; Åkerstedt et al., 1991; Kecklund, 1996)

Interestingly, day sleep does not seem to improve much across series of night shifts (Foret and Benoit, 1978; Dahlgren, 1981b). It appears, however, that night workers sleep slightly better (longer) than rotating workers on the night shift (Kripke et al., 1971; Bryden and Holdstock, 1973; Tepas et al., 1981). The long term effects of shift work on sleep are rather poorly understood. However, Dumont (1988) found that the amount of sleep/wake and related disturbances in present day workers were positively related to their previous experience of night work. Guilleminault (1982) found an overrepresentation of former shift workers with different clinical sleep/wake disturbances appearing at a sleep clinic. Recently, we have shown that in pairs of twins discordant on night work exposure, the exposed twin reports somewhat deteriorated sleep quality and health after retirement (Ingre and Åkerstedt, in press).

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The main reason for the short daytime sleep is the influence exerted by the circadian rhythm. The more sleep is postponed from the evening towards noon next day, the more truncated it becomes and when noon is reached the trend reverts (Foret and Lantin, 1972; Åkerstedt and Gillberg, 1981) . Thus, sleep during the morning hours is strongly interfered with, despite the sizeable sleep loss that, logically, should enhance the ability to maintain sleep. (Czeisler et al., 1980). Also homeostatic influences control sleep. For example, the expected 4-5 hours of daytime sleep, after a night spent awake, will be reduced to 2 hours if a normal night sleep precedes it and to 3.5 hours if a 2-hour nap is allowed (Åkerstedt and Gillberg, 1986). Thus, the time of sleep termination depends on the balance between the circadian and homeostatic influences. The circadian homeostatic regulation of sleep has also been demonstrated in great detail in studies of forced or spontaneous desynchronization under conditions of temporal isolation and ad lib sleep hours (Czeisler et al., 1980; Dijk and Czeisler, 1995).

Alertness, performance and safety

Night oriented shift workers complain as much of fatigue and sleepiness as they do about disturbed sleep (Åkerstedt, 1988). The sleepiness is particularly severe on the night shift, hardly appears at all on the afternoon shift, and is intermediate on the morning shift. The maximum is reached towards the early morning (0500h to 0700h). Frequently, incidents of falling asleep occur during the night shift (Prokop and Prokop, 1955; Kogi and Ohta, 1975; Coleman and Dement, 1986). At least 2/3 of the respondents report that they have experienced involuntary sleep during night work.

Ambulatory EEG recordings verify that incidents of actual sleep occur during night work in, for example, process operators (Torsvall et al., 1989) . Other groups, such as train drivers or truck drivers show clear signs of falling-asleep incidents while driving at night (Caille and Bassano, 1977; Torsvall and Åkerstedt, 1987; Kecklund and Åkerstedt, 1993). This occurs towards the second half of the night and appears as repeated bursts of alpha and theta EEG activity, together with closed eyes and slow undulating eye movements. As a rule the bursts are short (1-15 seconds) but frequent, and seem to reflect let-downs in the effort to fend off sleep. Approximately 1/4 of the subjects recorded show the EEG/EOG patterns of fighting with sleep. This is clearly a larger proportion than what is is found in the subjective reports of falling asleep episodes.

As may be expected, sleepiness on the night shift is reflected in **performance**. One of the classics in this area is the study by Bjerner et al (1955) who showed that errors in meter readings over a period of 20 years in a gas works had a pronounced peak on the night shift. There was also a secondary peak during the afternoon. Similarly, Brown (1949) demonstrated that telephone operators connected calls considerably slower at night. Hildebrandt et al (1974) found that train drivers failed to operate their alerting safety device more often at night than during the day. Most other studies of performance have used laboratory type tests and demonstrated, for example, reduced reaction time or poorer mental arithmetic on the night shift (Tepas et al., 1981; Tilley et al., 1982). Flight simulation studies have, furthermore shown that the ability to "fly" a simulator (Klein et al., 1970), or to carry out a performance test (Dawson and Reid, 1997) at night may decrease to a level corresponding to that after moderate alcohol consumption (>0.05% blood alcohol) Interestingly, Wilkinson et al (1989) demonstrated that reaction time performance on the night shift (nurses) was better in permanent than rotating shift workers.

If sleepiness is severe enough, interaction with the environment will cease and if this coincides with a critical need for action an **accident** may ensue. Such potential performance lapses due to night work sleepiness were seen in several of the train drivers discussed earlier (Torsvall and Åkerstedt, 1987). The transport area is where most of the available accident data on night shift sleepiness has been obtained (Lauber and Kayten, 1988). Thus Harris (Harris, 1977) and

Hamelin (1987) demonstrated that single vehicle accidents have, by far, the greatest probability of occurring at night. So does fatigue-related accidents (Horne and Reyner, 1995) but also most other types of accidents, for example head-on collisions, rear end collisions (Åkerstedt et al., 2001). The National Transportation Safety Board ranks fatigue as one of the major causes of heavy vehicle accidents (NTSB, 1995).

From conventional industrial operations very little relevant data is available but fatal work accidents show a higher risk in shift workers (Åkerstedt et al., 2002a) and accidents in the automotive industry may exhibit night shift effects (Smith et al., 1994) and an interesting analysis has been put forward by the Association of Professional Sleep Societies' Committee on Catastrophies, Sleep and Public Policy (Mitler et al., 1988). Their consensus report notes that the nuclear plant meltdown at Chernobyl occurred at 0135h and was due to human error (apparently related to work scheduling). Similarly, the Three Mile Island reactor accident occurred between 0400h and 0600h and was due to, not only the stuck valve that caused a loss of coolant water but, more importantly, to the failure to recognize this event leading to the near meltdown of the reactor. Similar incidents, although with the ultimate stage being prevented, occurred 1985 at he David Beese reactor in Ohio and at the Rancho Seco reactor in California. Finally, the committee also states that the NASA Challenger space shuttle disaster stemmed from errors in judgement made in the early morning hours by people who had insufficient sleep (through partial night work) for days prior to the launch. Still, there is very limited support for the notion that shift work outside the transport area actually carries a higher over all accident risk.

As with sleep, the two main factors behind sleepiness and performance impairment are circadian rand homeostatic factors. Their effects may be difficult to separate in field studies but are clearly discernible in laboratory sleep deprivation studies (Fröberg et al., 1975) as well as in studies of forced desynchronization (Dijk et al., 1992). Alertness falls rapidly after awakening but gradually levels out as wakefulness is extended. The circadian influence appears as a sine-shaped superimposition upon this exponential fall in alertness. Space does not permit a discussion of the derivation of these functions, but the reader is referred to Folkard and Åkerstedt (Folkard and Åkerstedt, 1991) in which the "three-process model of alertness regulation is described. This model has been turned into computer software for predicting alertness and performance and to some extent accident risk.

Health effects

Gastrointestinal complaints are more common among night-shift workers than among day workers. In a review of a number of reports covering 34047 persons with day or shift work was found ulcers occurring in 0.3%-0.7% in day workers, in 5% of persons with morning and afternoon shifts, in 2.5-15% of persons with rotating shift systems with night shifts, and in 10%-30% in ex-shift workers (Angersbach et al., 1980). Several other studies have come to similar conclusions (Thiis-Evensen, 1958; Segawa et al., 1987; Harrington, 1994) Other gastrointestinal disorders, including gastritis, duodenitis and dysfunction of digestion are more common in shift workers than in day workers (Koller, 1983).

The pathophysiologic mechanism underlying gastrointestinal disesease in shift workers is unclear, but one possible explanation is that intestinal enzymes and intestinal mobility are not synchronized with the sleep/wake pattern. Intestinal enzymes are secreted with circadian rhythmicity, and shift workers' intake of food is irregular compared with intestinal function (Suda and Saito, 1979; Smith et al., 1982). A high nightly intake of food may be related to increased lipid levels (Lennernäs et al., 1994) and eating at the circadian low point may be associated with altered metabolic responses (Hampton et al., 1996). In addition, reduced sleep affects lipid and glucose metabolism (Spiegel et al., 1999).

A number of studies have reported a higher incidence of cardiovascular disease, especially coronary heart disease, in male shift workers than in men who work days (for review see (Kristensen, 1989; Bøggild and Knutsson, 1999). In a study of 504 paper mill workers followed for 15 years was found a dose-response relationship between years of shift work and incidence of coronary heart disease in the exposure interval 1-20 years of shift work (Knutsson et al., 1986). A study of 79000 female nurses in the United States gave similar results (Kawachi et al., 1995) as did a study with more than 1 million Danish men (Tüchsen, 1993) and a cohort of Finnish workers (Tenkanen et al., 1997). As with gastrointestinal disease, a high prevalence of smoking among among shift workers, might contribute to the increased risk of coronary heart disease, but smoking alone cannot explain the observed overrisk (Knutsson, 1989b). Another possibility is disturbances of metabolic parameters such as lipids and glucose for which there is some support as discussed above.

Only a few studies have addressed the issue of **pregnancy outcome** in shift workers. In one study of laboratory employees shift work during pregnancy was related to a significantly increased risk of miscarriage (RR 3.2) (Axelsson et al., 1984). Another study of hospital employees also demonstrated an increased risk of miscarriage (RR=1.44, 95% CI 0.83-2.51) (Axelsson and Rylander, 1989). Lower birth weight of infants of mothers who worked irregular hours has been reported (Axelsson and Rylander, 1989; Nurminen, 1989). No teratogenic risk associated with shift work was reported (Nurminen, 1989).

The mortality of shift and day workers was studied by Taylor and Pocock (Taylor and Pocock, 1972), who studied 8603 male manual worker in England and Wales between 1956 and 1968. Day, shift, and ex-shift workers were compared with national figures. SMR can be calculated from observed and expected deaths reported in the paper. SMRs for deaths from all causes were 97, 101 and 119 for day, shift, and ex-shift workers respectively. Although the figures might indicate an increasing trend, the differences were not statistically significant. However, the reported SMR close to 100 is remarkable because the reference popoulation was the general male population. Most mortality studies concerned with occupational cohorts reveal SMRs lower than 100, implying a healthy worker´s effect (Harrington, 1978). The same study showed significantly increased incidence of neoplastic disease in shift workers (SMR 116). A danish study of 6.000 shift workers failed to demonstrate any excess mortality in shift workers (Bøggild et al., 1999).

Rather little evidence exists on the connection between shift work and cancer. The mortality study by Taylor and Pocock (Taylor and Pocock, 1972) reported a increased incidence of neoplasms in shift workers compared with the general population . A recent Danish case-control study reportd an increased risk of breast cancer among 30-45-year old women who worked mainly nights (Hansen, 2001). In 75.000 nurses those with more than 15 years of night work showed an increased risk of colorectal cancer (Schernhammer et al., 2003). If the results are confirmed a possible mechanism may be the low levels of the hormone melatonin, due to light exposure during the night with a subsequent suppression of melatonin.

Very few studies are available but Koller et al (1978) found a prevalence of endocrine and metabolic disease of 3.5% in shift workers and 1.5% in day workers. Kawachi et al found in a prospective study of shift workers that the age-standardized prevalence was 5.6% at 15 years of shift work experience compared with 3.5% for no exposure (Kawachi et al., 1995). Nagaya et al found that markers of insulin resistance was more frequent in shift workers above the age of 50 than in day workers (Nagaya et al., 2002). Other indicators, such as body mass index, glucose leves, etc give a rather inconclusive impression as indicated in a review by Böggild and Knutsson (Bøggild and Knutsson, 1999).

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Another contributing factor to gastrointestinal diseases might be the association between shift work and **smoking**. A number of studies have reported that smoking is more common among shift workers (Angersbach et al., 1980; Knutsson et al., 1988). Studies concerned with **alcohol** consumption comparing day workers and shift workers have produced conflicting results (Smith et al., 1982; Knutsson, 1989a; Romon et al., 1992) , probably due to local cultural habits. One study, which used g-Glutamyltransferase as marker of alcohol intake, did not indicate that the shift workers had higher intake of alcohol than the day workers (Knutsson, 1989a).

Sickness absence is often used as a measure of occupational health risks. However, sickness leave is influenced by many irrelevant factors and cannot be considered as a reliable measure of true morbidity. Studies on sickness abscence in day and shift workers have revealed conflicting results and there is no evidence that shift workers have more sickness abscence than day workers. For review, see (Harrington, 1978).

Shift system characteristics

Which aspects of shift work are the most problematic then? And which are most conducive to wellbeing? The area has been reviewed recently by, for example Knauth (1996).

As important as night work in causing difficulties is, in our opinion, so called "**quick changes**", that is, reduced time-between-shifts, often only 8 hours. Obviously, if sleep is reduced between shifts, fatigue is increased in the second shift (Knauth et al., 1983; Kurumatani et al., 1994; Totterdell and Folkard, 1990; Axelsson et al., in press). The reason for the quick changes is usually that one likes to compress the working week to gain longer sequences of time off.

Aside from the night shift *per se* an important shift system characteristic is the **number of night shifts in a row**. Most studies indicate that the circadian system and sleep do not adjust (improve) much across a series of night shifts Fröberg et al (1972; Åkerstedt, 1977; Chaumont et al., 1979; Dahlgren, 1981a; Minors and Waterhouse, 1985) . Not even in permanent night workers is there seen an improvement (Patkai et al., 1977; Åkerstedt et al., 1977; Folkard et al., 1978) . Thus, one would expect a long series of night shifts (>4) to be particularly taxing. Sanderson (1986) indeed found that rated alertness and general wellbeing in 3-shift workers improved when a 2-3 day rotation was substituted for the old 7 day rotation. On the whole, the advantage with rapid rotation is that the taxing night shift is not permitted to exert its influence for more than a limited period of time (Knauth, 1995). On the other hand, if it is of major importance that performance capacity remains high during the night it seems that a solution with permanent night shifts is preferrable, in combination with other teams that work a two shift system with morning and afternoon shifts only (Folkard, 1992; Wilkinson, 1992). The issue of speed of rotation is still debated, however, and there are arguments for advantages of permanent night work.

With respect to the **duration** of shifts there is a feeling among researchers an practitioners that the prevalence is increasing but there is a lack of quantitative data. Interestingly, long shifts seem popular since they permit long sequences of free time and reduced commuting. Still, most would be tempted to assume that problems would increase with increasing duration and there is support for this notion (Kelly and Schneider, 1982; Reid et al., 1993; Rosa and Colligan, 1989; Rosa, 1991; Wheeler et al., 1972). Also, in a study of accidents in truck drivers Hamelin (1987) demonstrated a U-shaped relation between hours driven and accidents, ie, after an initial "warm up" period accident risk was low, with an increase towards 11 hours of driving. On the other hand, many studies have failed to find negative effects, or have found even positive effects (Duchon et al., 1994; Mills et al., 1983; Peacock et al., 1983; Williamson et al., 1994; Persson et al., 2003). Folkard has suggested that there also is an increase in

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accident risk after 3 hours (Folkard, 1997). The reason for the contradictory results may due to differences in, for example, the number of consecutive shifts, start and stop times, and on work load. Clearly, those schedules that involve an accumulation of work give rise to a sleep deficit that is problematic and which further causes elevated sleepiness levels during work (Kogi et al., 1989; Rosa and Colligan, 1989). Furthermore, a combination of sleep deficit, due to too many consecutive shifts, and physically demanding work has been shown to be negative (Rosa and Bonnet, 1993). Other factors that are seen as potential dangers if combined with extended shifts are overtime, no opportunity to take unscheduled rests, paced jobs, and second jobs (Rosa, 1995). Thus, there seems to be no strong argument against moderate extensions (2-4h) of 8h shifts, at least not as long as work load is acceptable..

Another debated aspect of the shift schedule is its **direction of** rotation (Knauth, 1995)**.** Since the free - running period of the human sleep/wake cycle averages 25 hours and since it can be entrained by environmental time cues only within 1-2 hours of the free run period, phase delays are easier to accomplish than phase advances. For the rotating shift worker this implies that schedules that delay, ie, rotate clockwise (morning- afternoon- night) should be preferred to those that rotate counterclockwise. There has been, however, very few practical tests of this theory, particularly in relation to sleepiness. Still, Czeisler (1982) has demonstrated that a change from counter clockwise to clockwise rotation, together with a change from 7 day to 21 day rotation, improved production and wellbeing in 3-shift workers. Orth-Gomér (1983) found that a change in the same direction in rapidly (1 day) rotating police officers reduced blood pressure and improved wellbeing. It appears, that similar effects may be obtained simply by having the night shift moved from the start to the end of the shift cycle (Fredén et al., 1986). We believe that the present opinion on the topic of direction is that it might be of less importance than originally thought.

Individual differences and strategies

There has been many attempts to identify individuals who are more or less tolerant to shift work, but very few clear results have been obtained (Härmä, 1995). However, health problems in shift workers usually increase with age (Foret et al., 1981; Åkerstedt and Torsvall, 1981) . The problems also increase with increasing exposure to shift work (Foret et al., 1981; Åkerstedt and Torsvall, 1981; Koller, 1983; Dumont et al., 1987). Gender is not in itself necessarily related to shift work tolerance (Härmä, 1993). On the other hand the extra load of household work may put women at a disadvantage. Being a morning type person (as opposed to an evening type) is associated with poorer adjustment to shift work (Aanonsen, 1964; Folkard et al., 1979).

Similarly, rigidity of sleep patterns is associated with difficulties in shift work (Folkard et al., 1979; Costa et al., 1989). It is not clear, however, to what extent the self estimate of sleep rigidity simply represents a reaction to prior shift work (or other irregular work hours). Comparisons of individuals who differ in attitude to shift work show that a major factor behind the negative attitude is a perceived inability to obtain good quality sleep in after night shifts (Axelsson et al., in press). Interestingly, low testosterone levels characterize those with negative attitudes and these levels are directly related to disturbed sleep (Axelsson et al., 2003).

Interestingly, a good physical condition of the individual may facilitate shift work. Thus, Härme et al (1986)] had threeshift workers improve their physical fitness through a training program. This greatly reduced rated overall fatigue. Another factor that will exacerbate night work sleepiness is sleep pathology such as that associated with, for example, sleep apnea (Lavie et al., 1981) .

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A number of diseases have been considered incommensurate with shift work, for example, diabetes and ulcer (Rutenfranz, 1982; Costa, 1998) . There is, however, very little hard evidence that such diseases will exacerbate with shift work.
Conclusion

Shift work or similar arrangements of work hours clearly affects sleep and alertness and there is a moderate risk of cardiovascular and gastrointestinal disease. Other diseases such as cancer or diabetes may be related to shift work but the evidence is as yet rather weak.

Conclusions

The present review suggests that the risk of disturbed sleep increases with age but there also seems to be a recent stress related increase in sleep disturbances in young adults. The long term health consequences are not understood.

The relation between gender and disturbed sleep is confusing. Females, as a rule complain more of sleep problems, but do not exhibit any objective indications of more disturbed sleep at least not among otherwise healthy women. With increasing age the sleep of males deteriorate whereas that of women is relatively well upheld. Pregnancy, however, is a period of increased risk of disturbed sleep , whereas the menstrual cycle and menopause show less evidence of disturbed sleep. Clearly there is a great need of longitudinal research on gender and sleep and in particular on the possible health consequences around pregnancy.

Stress due to work or family seems to be one of the major causes of disturbed sleep. The effects on the risk of insomnia is well established, but reduced sleep in itself seems to yield the same physiological changes as stress. This suggests that several of the major civilization diseases in Europe and the US (diabetes, cardiovascular disease, burnout) could be mediated via disturbed sleep. This link clearly warrants longitudinal studies with interventions.

Shift workers constitute a group that suffers from disturbed sleep for most of their occupational life. The reason is the interference of work hours with the normal timing of sleep. This leads to an increased risk of accidents, directly due to excessive sleepiness, but also to cardiovascular and gastrointestinal disease, although it is not clear whether the latter effects are sleep related or due to circadian factors - or to a combination. Recent studies also suggest that breast cancer may result from shift work due to the effects of light on melatonin secretion. This still needs verification, however. Future research needs to identify countermeasures, the reasons for large individual differences in tolerance and the possible cancerogenic and other effects.

The conclusions above should be seen against the profound effects of reduced or fragmented sleep on the neuroendocrine (including glucose and lipid regulation) and immune systems as well as the effects on mortality, diabetes and cardiovascular disease.

Aanonsen, A. (1964). <u>Shift work and health.</u> Universitetsforlaget,Oslo.

Ahlberg-Hultén, G.K., Theorell, T. and Sigala, F. (1995). "Social support, job strain and musculoskeletal pain among female health care personnel." 21, 435-439.

Ancoli-Israel, S. and Roth, T. (1999). "Characteristics of insomnia in the United States: Results of the 1991 National Sleep Foundation survey. I." 22 Suppl.2, S347-S353.

Angersbach, D., Knauth, P., Loskant, H., Karvonen, M.J., Undeutsch, K. and Rutenfranz, J. (1980). "A retrospective cohort study comparing complaints and disease in day and shift workers." International Archives of Occupational and Environmental Health, 45, 127-140.

Arnetz, B., Andréasson, S., Strandberg, M., Eneroth, P., Kallner, A. and Theorell, T. (1986). "Läkares arbetsmiljö: psykosociala, fysikaliska samt fysiologiska data från en strukturerad djupintervju och biokemisk undersökning av allmänläkare och allmänkirurger." Stressforskningsrapport, IPM, Nr 187,

Axelsson, G., Lutz, C. and Rylander, R. (1984). "Exposure to solvents and outcome of pregnancy in university laboratory employees." British Journal of Industrial Medicine, 41, 305-312.

Axelsson, G. and Rylander, R. (1989). "Outcome of pregnancy in relation to irregular and inconvenient work schedules." British Journal of Industrial Medicine, 46, 306-312.

Axelsson, J., Åkerstedt, T., Kecklund, G., Lindqvist, A. and Attefors, R. (2003). "Hormonal changes in satisfied and dissatisfied shift workers across a shift cycle." 95, 2099-2105.

Axelsson, J., Åkerstedt, T., Kecklund, G. and Lowden, A. (in press). "Tolerance to shift work - how does it relate to sleep and wakefullness?"

Axelsson, J., Åkerstedt, T., Kecklund, G. and Lowden, A. (submitted). "Satisfaction with shift work and its determinants."

Bixler, E.O., Kales, A. and Soldatos, C.R. (1979). "Sleep disorders encountered in medical practice: A national survey of physicians." Behavioral Medicine, 1-6.

Bjerner, B., Holm, Å. and Swensson, Å. (1955). "Diurnal variation of mental perfomance. A study of three-shift workers." British Journal of Industrial Medicine, 12, 103-110.

Bliwise, D.L. (1993). "Sleep in Normal Aging and Dementia." 16, 40-81.

Bonnet, M.H. (1985). "Effect of sleep disruption on sleep, performance, and mood." Sleep, 8, 11-19.

Bonnet, M.H. (1986a). "Performance and sleepiness as a function of frequency and placement of sleep disruption." Psychophysiology, 23, 263-271.

Bonnet, M.H. (1986b). "Performance and sleepiness following moderate sleep disruption and slow wave sleep deprivation." Physiology and Behavior, 915-918.

Brown, R.C. (1949). "The day and night performance of teleprinter switchboard operators." Journal of Occupational Psychology, 23, 121-126.

Bryden, G. and Holdstock, T.L. (1973). "Effects of night duty on sleep patterns of nurses." Psychophysiology, 10, 36-42.

Bøggild, H. and Knutsson, A. (1999). "Shift work, risk factors and cardiovascular disease." 25, 85-99.

Bøggild, H., Suadicani, P., Hein, H.O. and al, e. (1999). "Shift work, social class, and ischaemic heart disease in middle aged and elderly men: a 22 year follow up in the Copenhagen Male Study." 56, 640-645.

Caille, E.J. and Bassano, J.L. (1977). "Validation of a behavior analysis methodology: variation of vigilance in night driving as a function of the rate of carboxyhemoglobin", in Vigilance (Eds. R.R. Mackie), pp. 59-72, Plenum Press, New York.

Chaumont, A.J., Laporte, A., Nicolai, A. and Reinberg, A. (1979). "Adjustment of shift workers to a weekly rotation." Chronobiologia, 6(suppl), 27-36.

Coleman, R.M. and Dement, W.C. (1986). "Falling asleep at work: a problem for continous operations." Sleep Research, 15, 265.

Costa, G. (1998). "Guidelines for the medical surveillance of shift workers." 24, 151-155.

Costa, G., Lievore, F., Casaletti, G. and Gaffuri, E. (1989). "Circadian characteristics influencing interindividual differences in tolerance and adjustment to shift work." Ergonomics, 32, 373-385.

Czeisler, C.A., Moore-Ede, M.C. and Coleman, R.M. (1982). "Rotating shift work schedules that disrupt sleep are improved by applying circadian principles." Science, 217, 460-463.

Czeisler, C.A., Weitzman, E.D., Moore-Ede, M.C., Zimmerman, J.C. and Knauer, R.S. (1980). "Human sleep: its duration and organization depend on its circadian phase." Science, 210, 1264-1267.

Dahlgren, K. (1981a). "Adjustment of circadian rhythms and EEG sleep functions to day and night sleep among permanent night workers and rotating shift workers." Psychophysiology, 18, 381-391.

Dahlgren, K. (1981b). "Long-term adjustment of circadian rhythms to a rotating shiftwork schedule." Scandinavian Journal of Work, Environment, and Health, 7, 141-151.

Dawson, D. and Reid, K. (1997). "Fatigue, alcohol and perfomance impairment." 388, 235-235.

Dew, M.A., Hoch, C.C., Buysse, D.J., Monk, T.H., Begley, A.E., Houck, P.R., Hall, M., Kupfer, D.J. and Reynolds, C.F. (2003). "Healthy older adults' sleep predicts all-cause mortality at 4 to 19 years of follow-up." 65, 63-73.

Dijk, D.-J. and Czeisler, C.A. (1995). "Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans." The Journal of Neuroscience, 15, 3526-3538.

Dijk, D.-J. and Duffy, J.F. (1999). "Circadian regulation of human sleep and age-related changes in its timing." 31, 130-140.

Dijk, D.-J., Duffy, J.F., Shanahan, T.L. and Czeisler, C.A. (1999). "Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms." 516, 611-627.

Dijk, D.J., Beersma, D.G.M. and Bloem, G.M. (1989a). "Sex differences in the sleep EEG of young adults: Visual scoring and spectral analysis." Sleep, 12, 500-507.

Dijk, D.J., Beersma, G.M. and Van den Hofdakker, R.H. (1989b). "All night spectral analysis of EEG sleep in young adult and middle-aged male subjects." Neurobiology of aging, 10, 677-682.

Dijk, D.J., Duffy, J.F. and Czeisler, C.A. (1992). "Circadian and sleep-wake dependent aspects of subjective alertness and cognitive performance." Journal of Sleep Research, 1, 112-117.

Dinges, D.F., Pack, F., Williams, K., Gillen, K.A., Powell, J.W., Ott, G.E., Aptowicz, C. and Pack, A.I. (1997). "Cumulative sleepiness, mood disturbance,

and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night." 20, 267-277.

Duchon, J.C., M, K.C. and Smith, T. (1994). "Extended workdays in an underground mine: A work performance analysis." Human Factors, 36, 258-268.

Dumont, M., Montpaisir, J. and Infant-Rivard, C. (1987). "Past experience of nightwork and present quality of life." Sleep Research, 16, 40.

Dumont, M., Montplaisir, J. and Infante-Rivard, C. (1988). "Insomnia symptoms in nurses with former permanent nightwork experience", in Sleep '86 (Eds. W.P. Koella, F. Obal, H. Schulz and P. Visser), pp. 405-406, Gustav Fischer Verlag, Stuttgart.

Ehlers, C.L. and Kupfer, D.J. (1997). "Slow-wave sleep: Do young adult men and women age differently?" 6, 211-215.

Fabsitz, R.R., Sholinsky, P. and Goldberg, J. (1997). "Correlates of sleep problems among men: The vietnam era twin registry." 6, 50-60.

Folkard, S. (1992). "Is there a "best compromise" shift system?" Ergonomics, 35, 1453-1463.

Folkard, S. (1997). "Black times: Temporal determinants of transport safety." 29, 417-430.

Folkard, S., Monk, T.H. and Lobban, M.C. (1978). "Short and long term adjustment of circadian rhythms in "permanent" night nurses." Ergonomics, 21, 785-799.

Folkard, S., Monk, T.H. and Lobban, M.C. (1979). "Towards a predictive test of adjustment to shift work." Ergonomics, 22, 79-91.

Folkard, S. and Åkerstedt, T. (1991). "A three process model of the regulation of alertness and sleepiness", in Sleep, Arousal and Performance: Problems and Promises (Eds. R. Ogilvie and R. Broughton), pp. 11-26, Birkhäuser, Boston.

Foret, J. and Benoit, O. (1974). "Structure du sommeil chez des travailleurs à horaires alternants." Electroencephalography and Clinical Neurophysiology, 37, 337-344.

Foret, J. and Benoit, O. (1978). "Shiftwork: The level of adjustment to schedule reversal assessed by a sleep study." Waking and Sleeping, 2, 107-112.

Foret, J., Bensimon, B., Benoit, O. and Vieux, N. (1981). "Quality of sleep as a function of age and shift work", in Night and shift work: biological and social

aspects (Eds. A. Reinberg, N. Vieux and P. Andlauer), pp. 149-154, Pergamon Press, Oxford.

Foret, J. and Lantin, G. (1972). "The sleep of train drivers: An example of the effects of irregular work schdules on sleep", in Aspects of Human Efficiency. Diurnal Rhythm and Loss of Sleep (Eds. W.P. Colquhoun), pp. 273-281, The English Universities Press Ltd, London.

Fredén, K., Åkerstedt, T., Olssen, K. and Orth-Gomér, K. (1986). "Positive effects of displacing night work to the end of the shift cycle", in Night and shift work: longterm effects and their prevention (Eds. M. Haider, M. Koller and R. Cervinka), pp. 453-457, Peter Lang, Frankfurt am Main.

Fröberg, J., Karlsson, C.G., Levi, L. and Lidberg, L. (1975). "Circadian variations of catecholamine excretion, shooting range performance and self-ratings of fatigue during sleep deprivation." Biological Psychology, 2, 175-188.

Fröberg, J.E., Karlsson, C.G. and Levi, L. (1972). "Shift work. A study of catecholamine excretion, self-ratings and attitudes." Studia Laboris Salutis, 11, 10-20.

Geroldi, C., Frisoni, G.B., Rozzini, R., De Leo, D. and Trabucchi, M. (1996). "Principal lifetime occupation and sleep quality in the elderly." 42, 163-169.

Gillberg, M. and Åkerstedt, T. (1998). "Sleep loss and performance: No "safe" duration of a monotonous task." 64, 599-604.

Grossi, G., Perski, A., Evengård, B., Blomkvist, V. and Orth-Gomér, K. (In press). "Physiological correlates of burnout among women."

Guilleminault, C., Czeisler, S., Coleman, R. and Miles, L. (1982). "Circadian rhythm disturbances and sleep disorders in shift workers (EEG Supl no. 36)", in Kyoto Symposia (Eds. P.A. Buser, W.A. Cobb and T. Okuma), pp. 709-714, Elsevier, Amsterdam.

Hall, M., Buysse, D.J., Nowell, P.D., Nofzinger, E.A., Houck, P., Reynolds, C.F. and Kupfer, D.J. (2000). "Symptoms of Stress and Depression as Correlates of Sleep in Primary Insomnia." 62, 227-230.

Hamelin, P. (1987). "Lorry driver's time habits in work and their involvement in traffic accidents." Ergonomics, 30, 1323-1333.

Hampton, S.M., Morgan, L.M., Lawrence, N., Anastasiadou, T., Norris, F., Deacon, S., Ribeiro, D. and Arendt, J. (1996). "Postprandial hormone and metabolic responses in simulated shift work." 151, 259-267.

171

Hansen, J. (2001). "Light at Night, Shiftwork, and Breast Cancer Risk." 93, 1513-1515.

Harrington, J.M. (1978). Shift work and health. A critical review of the literature. HMSO,London.

Harrington, J.M. (1994). "Shift work and health - a critical review of the literature on working hours." 23, 699-705.

Harris, W. (1977). "Fatigue, circadian rhythm and truck accidents", in Vigilance (Eds. R.R. Mackie), pp. 133-146, Plenum Press, New York.

Hildebrandt, G., Rohmert, W. and Rutenfranz, J. (1974). "12 and 24 hour rhytms in error frequency of locomotive drivers and the influence of tiredness." International Journal of Chronobiology, 2, 175-180.

Horne, J.A. and Reyner, L.A. (1995). "Sleep related vehicle accidents." British Medical Journal, 310, 565-567.

Hume, K.I., Van, F. and Watson, A. (1998). "A field study of age and gender differences in habitual adult sleep." 7, 85-94.

Härmä, M. (1993). "Individual differences in tolerance to shiftwork: a review." Ergonomics, 36, 101-109.

Härmä, M. (1995). "Sleepiness and shiftwork: individual differences." 4 (suppl 2), 57-61.

Härmä, M.I., Ilmarinen, J., Knauth, P., Rutenfranz, J. and Hänninen, O. (1986). "The effect of physical fitness intervention on adaptation to shiftwork", in Night and shift work: longterm effects and their prevention (Eds. M. Haider, M. Koller and R. Cervinka), pp. 221-228, Peter Lang, Frankfurt am Main.

Ingre, M. and Åkerstedt, T. (in press). "Effect of accumulated night work during the working lifetime, on subjective health and sleep in monozygotic twins."

Karacan, I., Thornby, J.I., Anch, M., Holzler, C.E., Warheit, G.J., Schivab, J.J. and Williams, R.L. (1976). "Prevalence of sleep disturbances in a primarily urban Florida county." Social Science and Medicine, 10, 239-244.

Kawachi, I., Colditz, G.A., Stampfer, M.J., Willett, W.C., Manson, J.E., Speizer, F.R. and Hennekens, C.H. (1995). "Prospective study of shift work and risk of coronary heart desease in women." 92, 3178-3182.

Kecklund, G. (1996). "Sleep and alertness: Effects of shift work, early rising, and the sleep environment (PhD-thesis)." 252, 1-94.

Kecklund, G. and Åkerstedt, T. (1993). "Sleepiness in long distance truck driving: an ambulatory EEG study of night driving." Ergonomics, 36, 1007-1017.

Kecklund, G. and Åkerstedt, T. (1997). "Objective components of individual differences in subjective sleep quality." 6, 217-220.

Kelly, R. and Schneider, M. (1982). "The twelve-hour shift revisited: Recent trends in the electric industry." 11, 369-384.

Klein, D.E., Brüner, H. and Holtman, H. (1970). "Circadian rhytm of pilot's efficiency, and effects of multiple time zone travel." Aerospace Medicine, 41, 125-132.

Knauth, P. (1995). "Speed and direction of shift rotation." 4 (suppl 2), 41-46.

Knauth, P. (1996). "Design of shiftwork systems", in Shiftwork. Problems and solutions. (Eds. W.P. Colquhoun, G. Costa, S. Folkard and P. Knauth), pp. 155-173, Peter Lang GmbH, Frankfurt am Main.

Knauth, P., Kiesswetter, E., Ottman, W., Karvonen, M.J. and Rutenfranz, J. (1983). "Time-budget studies of policemen in weekly or swiftly rotating shift systems." Applied Ergonomics, 14, 247-252.

Knutsson, A. (1989a). "Relationships between serum triglycerides and g-Glutamyltransferase among shift and day workers." Journal of Internal Medicine, 226, 337-339.

Knutsson, A. (1989b). "Shift work and coronary heart disease." Scandinavian Journal of Social Medicine, 544, 1-36.

Knutsson, A., Åkerstedt, T. and Jonsson, B. (1988). "Prevalence of risk factors for coronary artery disease among day and shift workers." Scandinavian Journal of Work, Environment and Health, 14, 317-321.

Knutsson, A., Åkerstedt, T., Jonsson, B.G. and Orth-Gomér, K. (1986). "Increased risk of ischemic heart disease in shift workers." The Lancet, 12;2, 89-92.

Kogi, K. and Ohta, T. (1975). "Incidence of near accidental drowsing in locomotive driving during a period of rotation." Journal of Human Ergology, 4, 65-76.

Kogi, K., Ong, C.N. and Cabantog, C. (1989). "Some social aspects of shift work in Asian developing countries." 4, 151-159.

173

Koller, M. (1983). "Health risks related to shift work." International Archives of Occupational and Environmental Health, 53, 59-75.

Koller, M., Kundi, M. and Cervinka, R. (1978). "Field studies of shift work at an Austrian oil refinery. I. Health and psychosocial wellbeing of workers who drop out of shift work." Ergonomics, 21, 835-847.

Kripke, D.F., Cook, B. and Lewis, O.F. (1971). "Sleep of night workers: EEG recordings." Psychophysiology, 7, 377-384.

Kripke, D.F., Garfinkel, L., Wingard, D.L., Klauber, M.R. and Marler, M.R. (2002). "Mortality associated with sleep duration and insomnia." 59, 131-136.

Kripke, D.F., Simons, R.N., Garfinkel, L. and Hammond, E.C. (1979). "Short and long sleep and sleeping pills." Archives of General Psychiatry, 36, 103-116.

Kristensen, T.S. (1989). "Cardiovascular diseases and the work environment." Scandinavian Journal of Work, Environment, and Health, 15, 165-179.

Kuppermann, M., Lubeck, D.P., Mazonson, P.D., Patrick, D.L., Stewart, A.L., Buesching, D.P. and Fifer, S.K. (1995). "Sleep problems and their correlates in a working population." 10, 25-32.

Kurumatani, N., Koda, S., Nakagiri, S., Hisashige, A., Sakai, K., Saito, Y., Aoyama, H., Dejima, M. and Moriyama, T. (1994). "The effects of frequently rotating shiftwork on sleep and the family life of hospital nurses." Ergonomics, 37, 995-1007.

Kushnir, T. and Melamed, S. (1992). "The Gulf War and its impact on burnout and well-being of working civilians." 22, 987-995.

Lauber, J.K. and Kayten, P.J. (1988). "Sleepiness, circadian dysrhythmia, and fatigue in transportation system accidents." Sleep, 11, 503-512.

Lavie, P., Gertner, R., Zomer, J. and Podoshin, L. (1981). "Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis." Acta Oto-laryngologica, 92, 529-533.

Leger, D., Guilleminault, C., Dreyfus, J.P., Delahaye, C. and Paillard, M. (2000). "Prevalence of insomnia in a survey of 12 778 adults in France." 9, 35-42.

Leineweber, C., Kecklund, G., Janszky, I., Åkerstedt, T. and Orth-Gomér, K. (2003). "Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease. The Stockholm Female Coronary Risk Study." 54, 121-127.

Lennernäs, M., Åkerstedt, T. and Hambraeus, L. (1994). "Nocturnal eating and serum cholesterol of three-shift workers." Scandinavian Journal of Work Environment and Health, 20, 401-6.

Matsumoto, K. (1978). "Sleep patterns in hospital nurses due to shift work: An EEG study." Waking and Sleeping, 2, 169-173.

Melamed, S., Kushnir, T. and Shirom, A. (1992). "Burnout and Risk Factors for Cardiovascular Diseases." 18, 53-60.

Melamed, S., Ugarten, U., Shirom, A., Kahana, L., Lerman, Y. and Froom, P. (1999). "Chronic burnout, somatic arousal and elevated salivary cortisol levels." 46, 591-598.

Mills, M.E., Arnold, B. and Mooney Wood, C. (1983). "Core-12: a controlled study of the impact of 12-hour scheduling." Nursing Research, 32, 356-361.

Minors, D.S. and Waterhouse, J.M. (1985). "Circadian rhythms in deep body temperature, urinary excretion and alertness in nurses on night work." Ergonomics, 28, 1523-1530.

Mitler, M.M., Carskadon, M.A., Czeisler, C.A., Dement, W.C., Dinges, D.F. and Graeber, R.C. (1988). "Catastrophes, sleep and public policy: concensus report." Sleep, 11, 100-109.

Mitler, M.M., Miller, J.C., Lipsitz, J.J., Walsh, J.K. and Wylie, C.D. (1997). "The sleep of long-haul truck drivers." 337, 755-761.

Moline, M.L., Broch, L., Zak, R. and Gross, V. (2003). "Sleep in women across the life cycle from adulthood through menopause." 7, 155-177.

Morin, C.M., Rodrigue, S. and Ivers, H. (2003). "Role of stress, arousal, and coping skills in primary insomnia." 65, 259-267.

Nagaya, T., Yoshida, H., Takahashi, H. and Kawai, M. (2002). "Markers of insulin resistance in day and shift workers aged 30-59 years." 75, 562-8.

Nilsson, P., Nilsson, J.-Å., Hedblad, B. and Berglund, G. (2001). "Sleep disturbances in association with elevated pulse rate for the prediction ofmortality - Consequences of mental strain?" 250, 521-529.

Nilsson, P., Rööst, M., Engström, G., Hedblad, B., Janzon, L. and Berglund, G. (2002). Incidence of diabetes in middle-aged men is related to resting heart rate and difficulties to fall asleep. (Abstract). 7th International Congress of Behavioural Medcine.

175

North, F.M., Syme, L., Feeney, A., Shipley, M. and Marmot, M. (1996). "Psychosocial work environment and sickness absence among British civil servants: the Whitehall II study." 86, 332-340.

NTSB. (1995). "Factors that affect fatigue in heavy truck accidents." NTSB/SS-95/01,

Nurminen, T. (1989). "Shift work, fetal development and course of pregnancy." Scandinavian Journal of Work, Environment, and Health, 15, 395-403.

Orth-Gomér, K. (1983). "Intervention on coronary risk factors by adapting a shift work schedule to biological rhythmicity." Journal of Psychosomatic Medicine, 45, 407-415.

Parish, J.M. and Shepard, J.W. (1990). "Cardiovascular effects of sleep disroders." Chest, 97, 1220-1226.

Partinen, M., Eskelinen, L. and Tuomi, K. (1984). "Complaints of insomnia in different occupations." 10, 467-469.

Patkai, P., Åkerstedt, T. and Pettersson, K. (1977). "Field studies of shift work: I Temporal patterns in psychophysical activation in permanent night workers." Ergonomics, 20, 611-619.

Peacock, B., Glube, R., Miller, M. and Clune, P. (1983). "Police officers' responses to 8 and 12 hour shift schedules." Ergonomics, 325, 479-493.

Persson, R., Ørbæk, P., Ursin, H., Kecklund, G., Österberg, K. and Åkerstedt, T. (2003). "Effects of the implementation of an 84-hour workweek on neurobehavioral test performance and cortisol responsiveness during testing." 29, 261-269.

Prokop, O. and Prokop, L. (1955). "Ermüdung und Einschlafen am Steuer." Zentralblatt für Verkehrsmedizin, Verkehrspsychologie und angrenzende Gebiete., 1, 19-30.

Reid, N., Robinson, G. and Todd, C. (1993). "The quantity of nursing care on wards working 8- and 12-hour shifts." 30, 403-413.

RFV. (2003). Långtidssjukskrivna - egenskaper vid 2003 års RFV-LS-undersökning. 19.

Ribet, C. and Derriennic, F. (1999). "Age, Working Conditions, and Sleep Disorders: a Longitudinal Analysis in the French Cohort E.S.T.E.V." 22, 491-504.

Romon, M., Nuttens, M.C. and Fievet, C. (1992). "Increased triglyceride levels in shift workers." American Journal of Medicine, 259-262.

Rosa, R. (1995). "Extended workshifts and excessive fatigue." 4 (suppl 2), 51-56.

Rosa, R.R. (1991). "Performance, alertness, and sleep after 3.5 years of 12-hour shifts: A follow-up study." 5, 107-116.

Rosa, R.R. and Bonnet, M.H. (1993). "Performance and alertness on 8h and 12h rotating shifts at a natural gas utility." Ergonomics, 36, 1177-1193.

Rosa, R.R. and Colligan, M.J. (1989). "Extended workdays: effects of 8-hour and 12-hour rotating shift schedules on performance, subjective alertness, sleep patterns, and psychosocial variables." Work and Stress, 3, 21-32.

Rutenfranz, J. (1982). "Occupational health measures for night- and shiftworkers." Journal of Human Ergology, 11, suppl, 67-86.

Sateia, M., Doghramji, K., Hauri, P.J. and Morin, C.M. (2000). "Evaluation of chronic insomnia." 23, 243-263.

Schernhammer, E.S., Laden, F., Speizer, F.E., Willett, W.C., Hunter, D.J., Kawachi, I., Fuchs, C.S. and Colditz, G.A. (2003). "Night-shift work and risk of colorectal cancer in the nurses' health study." 95, 825-8.

Segawa, K., Nakazawa, S., Tsukamoto, Y., Kurita, Y., Goto, H., Fukui, A. and Takano, K. (1987). "Peptic ulcer is prevalent among shift workers." Digestive Diseases and Sciences, 32, 449-453.

Smith, L., Folkard, S. and Poole, C.J.M. (1994). "Increased injuries on night shift." 344, 1137-39.

Smith, M.J., Colligan, M.J. and Tasto, D.L. (1982). "Health and safety consequnces of shift work in the food-processing industry." Ergonomics, 25, 133-144.

Spiegel, K., Leproult, R. and Van Cauter, E. (1999). "Impact of sleep debt on metabolic and endocrine function." 354, 1435-1439.

Suda, M. and Saito, M. (1979). "Coordinative regulation of feeding behavior and metabolism by a circadian timing system", in Biological Rhythms and Their Central Mechanism (Eds. M. Suda, O. Hayaishi and H. Nakagawa), pp. 263-271, Elsevier/North-Hollan Biomedical, New York.

Taylor, P.J. and Pocock, S.J. (1972). "Mortality of shift and day workers 1956-68." British Journal of Industrial Medicine, 29, 201-207.

Tenkanen, L., Sjöblom, T., Kalimo, R., Alikoski, T. and Härmä, M. (1997). "Shift work occupation and coronary heart disease over 6 years of follow-up in the Helsinki Heart Study." 23, 257-265.

Tepas, D.I., Walsh, J.K., Moss, P.D. and Armstrong, D. (1981). "Polysomnographic correlates of shift worker performance in the laboratory", in Night and shift work: biological and social aspects (Eds. A. Reinberg, N. Vieux and P. Andlauer), pp. 179-186, Pergamon Press, Oxford.

Theorell, T., Tsutsumi, A., Hallquist, J., Reuterwall, C., Hogstedt, C., Fredlund, P., Emlund, N. and Johnson, J.V. (1998). "Decision latitude, job strain, and myocardial infarction: A study of working men in Stockholm." 88, 382-388.

Thiis-Evensen, E. (1958). "Shift work and health." Industrial Medicine and Surgery, 27, 493-497.

Tilley, A.J., Wilkinson, R.T. and Drud, M. (1981). "Night and day shifts compared in terms of the quality and quantity of sleep recorded in the home and performance measured at work: a pilot study", in Night and shift work. Biological and social aspects (Eds. A. Reinberg, N. Vieux and P. Andlauer), pp. 187-196, Pergamon Press, Oxford.

Tilley, A.J., Wilkinson, R.T., Warren, P.S.G., Watson, W.B. and Drud, M. (1982). "The sleep and performance of shift workers." Human Factors, 24, 624-641.

Torsvall, L. and Åkerstedt, T. (1987). "Sleepiness on the job: continuously measured EEG changes in train drivers." Electroencephalography and Clinical Neurophysiology, 66, 502-511.

Torsvall, L. and Åkerstedt, T. (1988). "Disturbed sleep while being on call. An EEG study of apprehension in ships' engineers." Sleep, 11, 35-38.

Torsvall, L., Åkerstedt, T., Gillander, K. and Knutsson, A. (1989). "Sleep on the night shift: 24-hour EEG monitoring of spontaneous sleep/wake behavior." Psychophysiology, 26, 352-358.

Totterdell, P. and Folkard, S. (1990). "The effects of changing from a weekly rotating to a rapidly rotating shift schedule", in Shiftwork: health, sleep and performance (Eds. G. Costa, G. Cesena, K. Kogi and A. Wedderburn), pp. 646-650, Verlag Peter Lang, Frankfurt am Main.

Tüchsen, F. (1993). "Working hours and ischaemic heart disease in Danish men: A 4-year cohort study of hospitalization." 22, 215-221.

Urponen, H., Vuori, I., Hasan, J. and Partinen, M. (1988). "Self-evaluations of factors promoting and disturbing sleep: An epidemiological survey in Finland." 26, 443-450.

Vgontzas, A.N., Bixler, E.O., Lin, H.-M., Prolo, P., Mastorakos, G., Vela-Bueno, A., Kales, A. and Chrousos, G.P. (2001). "Chronic Insomnia Is Associated with Nyctohemeral Acativation of the Hypothalamic-Pituitary-Adrenal Axis: Clinical Implication." 86, 3787-3794.

Vgontzas, A.N., Papanicolaou, D.A., Bixler, E.O., Hopper, K., Lotsikas, A., Lin, H.-M., Kales, A. and Chrousos, G.P. (2000). "Sleep Apnea and Daytime Sleepiness and Fatigue: Relation to Visceral Obesity, Insulin Resistance, and Hypercytokinemia." 85, 1151-1158.

Weber, A. and Jaekel-Reinhard, A. (2000). "Bournout syndrome: a disease of modern societies?" 50, 512-517.

Wheeler, K., Gurman, R. and Tarnowieski, D. (1972). "The four-day week", (Eds. pp. 1-41, American Management Association, N.Y., New York.

Wilkinson, R.T. (1992). "How fast should the night shift rotate?" Ergonomics, 35, 1425-1446.

Williams, R.L., Karacan, I. and Hursch, C.J. (1974). EEG of human sleep. John Wiley and Sons,New York.

Williamson, A.M., Gower, C.G.I. and Clarke, B.C. (1994). "Changing the hours of shiftwork: a comparison of 8- and12-hour shift rosters in a group of computer operators." Ergonomics, 37, 287-298.

Åkerstedt, T. (1977). "Inversion of the sleep wakefulness pattern: Effects on circadian variations in psychophysiological activation." Ergonomics, 20, 459-474.

Åkerstedt, T. (1987). "Sleep and stress", in Sleep related disorders and internal diseases (Eds. J.H. Peter, T. Podszus and P. von Wichert), pp. 183-191, Springer Verlag, Heidelberg.

Åkerstedt, T. (1988). "Sleepiness as a consequence of shift work." Sleep, 11, 17-34.

Åkerstedt, T. (1990). "Sleep and performance - an introduction", in Shift work: health, sleep and performance (Eds. G. Costa, G. Cesana, K. Kogi and A. Wedderburn), pp. 409-414, Peter Lang, Frankfurt am Main.

179

Åkerstedt, T., Fredlund, P., Gillberg, M. and Jansson, B. (2002a). "A prospective study of fatal occupational accidents - relationship to sleeping difficulties and occupational factors." 11, 69-71.

Åkerstedt, T., Fredlund, P., Gillberg, M. and Jansson, B. (2002b). "Work load and work hours in relation to disturbed sleep and fatigue in a large representative sample." 53, 585-588.

Åkerstedt, T. and Gillberg, M. (1981). "The circadian variation of experimentally displaced sleep." Sleep, 4, 159-169.

Åkerstedt, T. and Gillberg, M. (1986). "A dose-response study of sleep loss and spontaneous sleep termination." Psychophysiology, 23, 293-297.

Åkerstedt, T., Kecklund, G. and Hörte, L.-G. (2001). "Night Driving, Season, and the Risk of Highway Accidents." 24, 401-406.

Åkerstedt, T., Kecklund, G. and Knutsson, A. (1991). "Spectral analysis of sleep electroencephalography in rotating three-shift work." Scandinavian Journal of Work Environment and Health, 17, 330-336.

Åkerstedt, T., Knutsson, A., Westerholm, P., Theorell, T., Alfredsson, L. and Kecklund, G. (2002c). "Sleep disturbances, work stress and work hours. A cross-sectional study." 53, 741-748.

Åkerstedt, T. and Nilsson, P.M. (2003). "Sleep as restitution: an introduction." 254, 6-12.

Åkerstedt, T., Patkai, P. and Dahlgren, K. (1977). "Field studies of shift work: II. Temporal patterns in psychophysiological activation in workers alternating between night and day work." Ergonomics, 20, 621-631.

Åkerstedt, T. and Torsvall, L. (1981). "Age, sleep, and adjustment to shift work", in Sleep 1980 (Eds. W. Koella), pp. 190-194, Karger, Basel.

Annex 2 –Participants List

Prof Torbjörn Akerstedt
IPM Karolinska Institute
Sweden

Dr Wolfgang Babisch
Umweltbundesamt
Department of Environmental Hygiene
Germany

Prof Michel Billiard
Professor of Neurology
Université de Montpellier
France

Prof Oliviero Bruni
Università La Sapienza di Roma
Centro per i Disturbi del Sonno in Età evolutiva, Dip. Scienze Neurologiche
Italy

Prof Christopher L. Drake
Henry Ford Hospital Sleep Center, CFP-3
United States of America

Prof J.A. Horne
Loughborough University
Sleep Research Center
United Kingdom

Dr Ken Hume
Manchester Metropolitan University
Centre for Aviation, Transport and Environment
Dept. of Biological Sciences

Prof André Kahn
Université Libre de Bruxelles Clinique pédiatrique
Hôpital univ. des enfants Reine Fabiola
Belgium

Dr Damien Léger, M.D., PhD.
Hôtel Dieu de Paris, Université Paris 5
France

Prof Alain Muzet
CNRS-CEPA
21, rue Becquerel
France

Dr Sonia Nevsimalova
Charles University
Department of Neurology
Czech Republic

Prof Teresa Paiva
Hospital Santa Maria, Lab EEG/Sono, Dept of Neurology, Centro Estudos Egas Moniz
Portugal

Dr Michal Skalski
Katedra i Klinika Psychiatryczna
AM w Warszawie
Poland

Prof Stephen Stansfeld
Queen Mary University of London
Department of Psychiatry
United Kingdom

Prof Jan Trabka
Collegium Medicum UJ, Zaklad Biocybernetyki
Poland

Dr Marie-Francoise Vecchierini
Vice Presidente de la Societe Francaise de Recherche sur le Sommeil
Hôpital Bichat, Laboratoire de Sommeil
France

Dr Alfred Wiater
Krankenhaus Porz am Rhein
Kinderklini
Germany

Dr Henning Wulbrand
Eppendorf Center for Child Neurology
Germany

Dr Martin van den Berg
Spatial Planning and Environment (Ministry VROM)
Directorate for Local Environmental Quality (IPC 635)
The Netherlands

Observers

Dr med. Snezana Jovanovic
Landesgesundheitsamt Baden-Württemberg
Germany

Dr Christian Maschke
Forschungs- und Beratungsbüro Maschke
Germany

Dr Willy Passchier-Vermeer
Health Council of the Netherlands
Netherlands

World Health Organization

Regional Office for Europe

Mr Xavier Bonnefoy
WHO European Centre for Environment and Health, Bonn
Germany

Ms Célia Rodrigues
WHO European Centre for Environment and Health, Bonn
Germany

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