Institute of Clinical Medicine, Department of Psychiatry

University of Helsinki

SLEEP IN MENTAL AND BEHAVIOURAL DISORDERS

Nina Lindberg

Academic dissertation

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Supervised by:

Docent Tarja Stenberg, MD, PhD
University of Helsinki

and

Docent Björn Appelberg, MD, PhD
University of Helsinki

Reviewed by:

Professor Hannu Lauerma, MD, PhD
University of Turku

and

Docent Timo Partonen, MD, PhD
University of Helsinki
National Public Health Institute, Helsinki

Opponent:

Professor Pirkko Räsänen, MD, PhD
University of Oulu

Cover: Jonna Piipponen

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ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:

I. Nina Lindberg, Matti Virkkunen, Pekka Tani, Björn Appelberg, Ranan Rimón, Tarja Porkka-Heiskanen. GH-IGF-1 AXIS, LEPTIN AND SLEEP IN ANOREXIA NERVOSA PATIENTS. Neuropsychobiology, in press.

II. Nina Lindberg, Pekka Tani, Björn Appelberg, Dag Stenberg, Hannu Naukkarinen, Ranan Rimón, Tarja Porkka-Heiskanen, Matti Virkkunen. SLEEP AMONG HABITUALLY VIOLENT OFFENDERS WITH ANTISOCIAL PERSONALITY DISORDER. Neuropsychobiology, in press.

III. Nina Lindberg, Pekka Tani, Björn Appelberg, Hannu Naukkarinen, Ranan Rimón, Tarja Porkka-Heiskanen, Matti Virkkunen. HUMAN IMPULSIVE AGGRESSION: A SLEEP RESEARCH PERSPECTIVE. Journal of Psychiatric Research, in press.

IV. Nina Lindberg, Matti Virkkunen, Pekka Tani, Björn Appelberg, Jussi Virkkala, Ranan Rimón, Tarja Porkka-Heiskanen. EFFECT OF A SINGLE-DOSE OF OLANZAPINE ON SLEEP IN HEALTHY FEMALES AND MALES. International Clinical Psychopharmacology 2002: 17: 117–184.

ABBREVIATIONS

AN = anorexia nervosa
APA = American Psychiatric Association
ASP = antisocial personality disorder
ASPs = persons with antisocial personality disorder
AST = actual sleep time
BMI = body mass index
BNSQ = Basic Nordic Sleep Questionnaire
BPD = borderline personality disorder
CD = conduct disorder
CDT = carbohydrate deficient transferrin
EEG = electroencephalogram
EMG = electromyogram
EOG = electro-oculogram
GH = growth hormone
GT = gamma-glutamyl transferase
5-HT = 5-hydroxytryptamine = serotonin
IGF = insulin-like growth factor
IED = intermittent explosive disorder
IQ = intelligence quotient
PFC = prefrontal cortex
PSG = polysomnography
REM = rapid eye movement sleep
S1-S4 = sleep stages 1-4
SCID = Structured Clinical Interview for Disorder
SE = sleep efficiency
SEM = standard error of the mean
SPA = spectral power analysis
SWS = slow wave sleep
TST = total sleep time

SUMMARY

Disturbed sleep is a common complaint in psychiatric patients. Sleep problems can be either the cause or the consequence of psychiatric distress, and they may also appear together as a core symptom of a particular psychiatric diagnosis. In health care, it is often common practice to describe sleep medication for a psychiatric patient. In fact, the practice is often so automatic that a deeper understanding of the specific nature of the problem remains to be lost. However, it has been suggested that the appropriate intervention for sleep problems may either relieve the symptoms of the psychiatric disorder or in some cases even prevent them. The quality of sleep is constituted of many components, but one of the most important factors is its normal structure. This emphasizes the importance of studying the effects of psychiatric medication on sleep architecture. PSG, which is a time-consuming procedure requiring special expertise, can hardly be used as a standard method for all psychiatric patients with sleep problems. In some cases, however, it is has been shown to be useful and should be available in psychiatric hospitals for clinical use and not just as an academic research method. The less burdensome methods like actometry and static charge sensitive bed (SCSB) (Alihanka et al., 1981) should not be forgotten in clinical work.

Since the discovery of REM sleep in the 1950s, psychiatric sleep research has focused on the role of REM sleep by studying both the dreaming and the association between REM parameters and psychiatric disorders. However, the focus has recently shifted to SWS, which has been shown to be a sensitive indicator of both somatic and psychiatric disturbances. In this work, in spite of the difference in the chosen psychiatric disorders (AN and ASP), the changes in sleep parameters compared with healthy controls were seen in non-REM sleep, and particularly in SWS. The changes in REM sleep appear to be typically associated with major depression, the disorder, which was excluded from this work.

The abnormal sleep architecture may serve as a marker of specific pathology, as seen previously in narcolepsy. The high amount of S4 sleep in habitually violent offenders with ASP is an unusual phenomenon. This finding, although still preliminary, may prove to be a specific marker of brain pathology associated with extreme impulsive aggression.

1. INTRODUCTION

1.1. Normal human sleep

1.1.1. General

Human sleep consists of two main components, rapid eye movement sleep (REM) and non-REM sleep, the latter divided into stages 1–4 (S1–S4). S3 and S4 in non-REM sleep are defined as slow wave sleep (SWS), also called delta sleep or deep sleep. The four non-REM stages roughly parallel a depth of sleep continuum, with arousal thresholds generally at their lowest in S1 and at their highest in S4. A healthy adult enters sleep through non-REM sleep and REM does not occur until 80 minutes or more thereafter. In normal sleep, REM and non-REM sleep periods alternate cyclically throughout the night so, that deep sleep predominates in the first third of the night, while REM sleep predominates during the last third of the night (Borbély, 1986a). The duration of nocturnal sleep is dependent on a number of factors. Most young adults report sleeping approximately 7.5 hours a night on weekday nights and slightly longer, 8.5 h, on weekend nights. The variability of these figures from person to person and from night to night is, however, quite high (Carskadon and Dement, 2000). Although the exact functions of the different sleep stages are not known, it is generally accepted that SWS is the physiologically significant, refreshing part of sleep (Carskadon and Dement, 2000). REM sleep is associated with dreaming, based on vivid dream recall reported after approximately 80 % of arousals from this state of sleep (Dement and Kleitman, 1957).

1.1.2. Assessment of sleep

1.1.2.1. Sleep questionnaire

One of the best methods for obtaining an overview of the patient's subjective sleep quality is a retrospective sleep questionnaire (Spielman et al., 2000). Questionnaires have the advantage of being able quickly to summarize the sleep events that have occurred over a long period of time.

1.1.2.2. Sleep diary

Unlike sleep questionnaires, a sleep diary offers a prospective method for studying the patient's sleep behavior. Filling in a sleep diary directs the patient's attention to aspects of behaviour that might otherwise be overlooked and in some versions presents the information in a graphic format that allows the clinician quickly to survey large amounts of data (Spielman et al., 2000). Filling in a diary before the treatment also provides a baseline against which the treatment response can be measured.

1.1.2.3. Actometry

Actometry and actigraphy are used in the literature as synonyms for recording methods based on accelerometric sensors. They react to acceleration signals produced by body movements. The data that are collected are displayed on a computer and are

examined for activity versus inactivity and analysed for wakefulness versus sleep. Wrist actometry technology is based on the fact that during sleep, there is little movement, whereas, during wakefulness, there is increased movement. Wrist actometry has the advantage of being cost efficient, allowing the recording of sleep in natural environments, recording behaviour that occurs during both the night and the day, and recording for long time periods (Ancoli-Israel, 2000).

1.1.2.4. Polysomnography

The golden standard for the evaluation of the patient's sleep structure is polysomnography (PSG), which includes the electrophysiological recording of brain cortex activity by electroencephalography (EEG), eye movements by electro-oculography (EOG), and skeletal muscle tone by electromyography (EMG). The recordings can be visually scored as either wakefulness or different stages of sleep (S1-S4, REM) in epochs of 30 seconds (Rechtschaffen and Kales, 1968) in order to draw a patient's sleep histogram. A PSG provides a great deal of information about the chosen study night.

1.1.2.5. Spectral power analysis

The EEG spectral power analysis (SPA) is used to provide more accurate information about sleep than traditional PSG; while the sleep scoring is based on a subjective evaluation of the recording, SPA is fully computerized. It quantitates the amplitude of different frequency bands (beta, sigma, alpha, theta and delta) of the EEG recording.

1.1.3. Sleep regulation

1.1.3.1. The two-process model

According to a current and widely accepted model of non-REM sleep regulation, sleeping is controlled by two separate components: circadian process C, which affects the appropriate timing of sleep and homeostatic process S, which accounts for a sufficient amount of sleep (Borbély, 1982). The circadian process C is mainly controlled by the rhythmic activity of the suprachiasmatic nucleus in the hypothalamus. In the case of the homeostatic process S, no single locus has been found in the central nervous system. It appears instead to be controlled by several neural systems, which are localized in the hypothalamus, basal forebrain, and brain stem nuclei (Borbély and Tobler, 1989).

1.1.3.2. Neurotransmitters regulating sleep

The biochemical regulation of sleep can be divided into *three* functionally different domains. *The wake promoting system* includes the classic aminergic neurotransmitters serotonin, noradrenaline and histamine as well as acetylcholine. The pontine monoaminergic nuclei and hypothalamic histaminergic neurons have the highest firing rate in waking, decreased in SWS and the lowest in REM sleep. The cholinergic neurons are an exception, as they have the same level of activity during both in waking and in REM sleep. Firing of midbrain dopaminergic neurons of the substan-

tia nigra and ventral tegmental area does not seem to vary in phase with the REM-NREM cycle, and it is supposed that the effects of dopamine on normal sleep might be mediated by its interactions with other neurotransmitter systems (Pace-Schott and Hobson, 2002). *The sleep promoting system* includes both the major inhibitory neurotransmitter gamma-aminobuturic acid (GABA), and adenosine, which has proved to be an important homeostatic factor. In cats, the accumulation of adenosine during wakefulness has been shown to induce sleep (Porkka-Heiskanen et al., 1997). *The modulatory factors* include a variety of molecules often of polypeptide structure, such as growth hormone (GH) (Jones, 2000).

1.1.4. The physiological significance of different frequency bins in the power spectrum

The spectral power in the delta range (0.5–3.5 Hz) correlates with the intensity ("depth") of stage 3+4 sleep, and can be used as an objective measure of the intensity of SWS (Borbély, 1986b). Low delta power is generally regarded as a sign of poor sleep quality, and delta power is reduced in many conditions, including mental disorders (Keshavan et al, 1995). Less is known about the correlates of the theta range (3.5–8.5 Hz), although reductions in theta power have been described in patients with schizophrenia, for example (Keshavan et al., 1998). Both delta and theta power decline across the night and increase with the duration of wakefulness preceding sleep as markers of the homeostatic sleep process (Borbély et al., 1981). The physiological roles of the higher frequency powers remain somewhat speculative at present. The delta, theta and sigma (12.0–14.5 Hz) powers have been reported to decrease and the beta (14.5–25 Hz) power to increase during aging by Carrier et al. (2001).

1.2. Sleep disturbances in the light of epidemiological studies

1.2.1. The prevalence of sleep disturbances

Disturbed sleep is a common complaint and source of distress in community surveys of self-reported health problems (Ohayon, 2002). Hublin et al. (1996) reported that, in the general Finnish adult population, 11.0% of women and 6.7 % of men suffered from daytime sleepiness every or almost every day. Insomnia at least every other day was reported by 20.7 % of women and 28.6 % of men. Among those with daytime sleepiness, 11 % used hypnotics or tranquillizers on more than 180 days per year. In the Swedish population, complaints of sleeping difficulties (i.e. pronounced difficulty in falling asleep, nocturnal awakenings, and/or premature morning awakenings) were reported by 15.3% of all subjects (Lindberg et al., 1997). Difficulty maintaining sleep, the absence of feeling refreshed in the morning, and excessive daytime sleepiness were more common among females than males. In an epidemiological study by Quera-Silva et al. (1991) in France, 10% of the population reported the use of hypnotics, with 6.2 % indicating frequent and chronic use for more than six months. The group who most frequently used hypnotics were women aged 45 years and older.

1.2.2. The co-morbidity of sleep problems and mental disorders

Bixler et al. (1979) conducted the first study, which included a section on mental disorders in interviews with persons with insomnia (difficulty in initiating or maintaining sleep). They found that 19.4 % of insomniacs had depression, 50% had emotional problems, and 35.7% had a recurring health problem. However, the study was based on the individual's own perception. In a survey of insomniacs investigated in general practice, Hohagen et al. (1993) using DSM III R criteria, found a high level of comorbidity for severe insomnia with psychiatric disorders. Of 150 severe insomniacs, 21.7% were diagnosed as having depression, 7.2% neurosis/personality disorders, 4.6% alcohol or drug abuse, 5.6% psychosomatic disorders, 1% psychosis, and 1.3% organic brain syndrome. When it came to the different diagnostic subgroups, severe insomnia was consistently shown to have a highly significant association with all psychiatric diagnoses, while moderate insomnia was only associated with the diagnosis of depression. In a study by Schramm et al. (1995), 50% of patients with current insomnia in general practice also had at least one additional current axis I or II diagnosis. Affective disorders were the most common principal psychiatric diagnosis, followed by substance abuse disorders. The predominant personality was characterized by avoidant, dependent, obsessive-compulsive and passive-aggressive features. In a study by Ford and Kamerow (1989), almost 8000 individuals were questioned about sleep complaints and psychiatric symptoms at baseline and one year later. The diagnoses were made using DSM III criteria. Of this community sample, 10.2% reported insomnia and 3.2% hypersomnia (excessive sleepiness) at the first interview. Forty per cent of those with insomnia and 46.5% of those with hypersomnia had a psychiatric disorder, compared with 16.4 % of those with no sleep complaints. The most common disorders in patients with sleep complaints were anxiety disorders including phobias, obsessive-compulsive disorder, and panic disorder. Depressive disorders and alcohol and drug abuse disorders were also common. The most important finding was that individuals with continuing insomnia had significantly higher rates of new cases of both major depression and anxiety disorders compared with those whose insomnia had been resolved. Individuals with continuing hypersomnia also had higher rates of new cases of major depression and anxiety disorders, although the numbers were smaller than those for individuals with insomnia. In a longitudinal epidemiological study of young adults by Breslau et al. (1996), lifetime associations with specific psychiatric disorders were as high for insomnia and hypersomnia, and persons with a history of both disturbances had higher rates of psychiatric disorders than those with either of the disturbances alone. The strongest lifetime association of sleep disturbance was major depression, even when a diagnosis of major depression was made on the basis of symptoms other than sleep disturbance. A history of either type of sleep disturbance at baseline signalled an increased risk of a new onset of major depression, illicit drug use disorder, and nicotine dependence. Breslau et al. pointed out that complaints of two weeks or more of insomnia almost every night could be regarded as a useful marker of the subsequent onset of major depression. Weissman et al. (1997) reported data from an epidemiological community survey of more than 10,000 adults. The major findings were that insomnia, even when uncomplicated by a psychiatric disorder, is associated with increased treatment seeking from the general medical or psychiatric speciality sectors, and with an increased risk of subsequent first onset of major depression, panic disorder, and alcohol

abuse one year later. The findings suggest that early intervention for insomnia may be an opportunity for preventing subsequent psychiatric disorders.

So, as Balter et al. (1992) concluded, "Sleep problems can be either the cause or the consequence of psychiatric distress. They can also appear together as a core symptom of a particular psychiatric diagnosis such as depression, post traumatic stress disorder and addiction". The relationship between sleep abnormalities and psychiatric disorders is not, however, clearly understood, in spite of many investigations, and more research has to be conducted in order to answer this difficult question more reliably (Léger, 2000).

1.3. The polysomnography in psychiatric disorders

Many investigations of sleep in psychiatric disorders over the past few decades have attempted to identify diagnostically sensitive and specific sleep patterns associated with particular disorders. Psychiatric sleep research has focused most intensively on REM latency reduction in affective disorders, as it appears to be most specific in distinguishing depressive patients from both normal subjects and those with other psychiatric disorders (Benca et al., 1992). Benca et al. reviewed a total of 177 studies using visual scoring methods with data for 7151 patients with different psychiatric disorders and controls in order to clarify the possible association between specific sleep patterns and psychiatric disorders. Most psychiatric groups displayed a significant reduction in sleep efficiency (SE) and total sleep time (TST), accounted for by decrements in non-REM sleep. REM sleep was relatively preserved in all groups, while REM % was increased in affective disorders. A reduction in REM latency was observed in affective disorders but occurred in other categories as well. Although no single sleep variable appeared to have absolute specificity for any particular psychiatric disorder, patterns of sleep disturbances associated with categories of psychiatric illnesses were observed. As the authors commented, further studies are needed to determine the diagnostic sensitivity and specificity of sleep disturbances in a variety of primary and secondary psychiatric disorders, their clinical usefulness, and the pathophysiological mechanisms of sleep disturbances in clinical disorders.

1.4. Sleep and schizophrenia

It is a well-known fact that one of the major symptoms of schizophrenia is sleep disturbance (Benson and Zarcone, 2000). The sleep of patients with schizophrenia is characterized by poor SE, which often takes the form of long sleep onset latencies and reduced total sleep. Sleep continuity is also impaired by long periods of waking after sleep onset (Ganguli et al., 1987; Tandon et al., 1992; Lauer et al., 1997). Reduced REM sleep latency, also reported in schizophrenia, has been attributed to cholinergic hyperactivity secondary to increased dopaminergic tone (Tandon et al., 1992). The secretion of prolactin is inhibited by dopamine. In a study by Appelberg et al. (2002) a positive correlation between serum prolactin levels and REM latency was found in patients with non-affective psychosis. It has been suggested that the reduction in SWS is the prevailing alteration in the sleep of patients with schizophrenia (Keshavan et al., 1995). The reduction in SWS tends to persist after the clinical

remission of psychotic symptoms (Maixner et al., 1998). Some correlation between the reduction in SWS and ventricle size in patients with schizophrenia has been reported (van Kammen et al., 1988; Lauer and Krieg, 1998). SPA reveals reductions in delta and theta power in patients with schizophrenia (Keshavan et al., 1998).

The fact that schizophrenia, as well as other psychotic disorders, is associated with serious sleep disturbances underlines the importance of finding antipsychotics, which are efficacious in inducing sleep, especially delta and theta sleep.

1.4.1. Olanzapine

Olanzapine is a novel antipsychotic medicine with proven efficacy in schizophrenia (Beasley et al., 1997). It has shown a high affinity for serotonin 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, histamine H1, dopamine D1, D2, D3, D4, alpha1-adrenergic and muscarinic receptor subtypes in vitro (Bymaster et al, 1999, 2001). In healthy volunteers and in patients with schizophrenia, olanzapine occupied more 5-HT2 receptors than D2-receptors in positron emission tomography (Nyberg et al., 1997; Kapur et al., 1999). In single- photon emission tomography (SPET) scan studies with a specific 5-HT2A ligand, increased binding in the frontal cortex compared with the cerebellum was seen in healthy subjects (Busatto et al., 1997). The pharmacological profile of olanzapine, with a prominent affinity for 5-HT2 and H1 receptors suggested that it may have hypnogenic effects on both patients with schizophrenia and healthy subjects.

1.4.2. Polysomnographic studies of olanzapine

Sálin-Pascual et al. (1999) described polysomnographic findings in 20 drug-free (at least two weeks before entering the study) patients with schizophrenia after the acute administration of 10 mg of olanzapine. They found significant increases in the total sleep time, REM density, S2 sleep and SWS. Sharpley et al. (2000) reported the effects of olanzapine on sleep in nine healthy males. Compared with placebo, both the 5-mg and 10-mg doses of olanzapine significantly increased SWS, sleep continuity measures, and subjective sleep quality. In addition, 10 mg of olanzapine suppressed REM sleep and increased REM sleep latency. The metabolism of drugs has been found to differ between the sexes (Poolsup et al., 2000), suggesting that medication may affect sleep differently among females and males. In the study by Sálin-Pascual et al. (1999), the patient group consisted of both females and males, but the results were not analysed separately. There are no published sleep EEG studies in which the effects of olanzapine on females are described.

1.5. Sleep in anorexia nervosa

Eating disorders are most prevalent during adolescence and young adulthood, respectively, an age range in which sleep tends to be least disturbed by psychiatric illness (Benca and Casper, 2000). Nevertheless, sleep disturbances are common in patients with AN and abnormalities in sleep architecture have been documented. Anorectics have been described as having shorter total sleep time, reduced SE, and more S1 sleep than controls (Crisp et al., 1971;Walsh et al., 1985; Levy et al., 1988). They

have also been reported as having less SWS (Neil et al., 1980; Levy et al., 1988), and a positive correlation between BMI and the amount of slow-wave activity in the delta range (0.5–4.5 Hz) has been reported (Nobili et al., 1999). Neil et al. (1980) and Katz et al. (1984) demonstrated shorter REM latency in AN compared with controls, while in many studies this phenomenon has not been observed (Walsh et al., 1985; Levy et al., 1988; Lauer and Krieg, 1992). The weight gain has increased total sleep duration as well as SWS (Crisp et al., 1971; Lacey et al., 1975; Lauer and Krieg, 1992).

1.5.1. The GH-IGF-1 axis and leptin in anorexia nervosa

Growth hormone (GH), a major anabolic hormone of the body, is secreted by the anterior pituitary gland. The synthesis and release of GH is controlled by the hypothalamus via two neurohormones, growth hormone releasing hormone (GHRH) and somatostatin. GHRH stimulates GH production and release and somatostatin inhibits them. The secretion of GH is pulsatile. The secretion bursts are flanked by almost undetectable levels of plasma GH. In humans, there is typically one high secretion pulse and a few lower ones during the 24-h day-night span (Van Cauter et al., 1998). Several studies report an increase in GH secretion, both basal and pulsatile, in anorectic patients (Scacchi et al., 1997; Stoving et al., 1999). In a study by Argente et al. (1997), two distinct groups of anorectics were found; those who hypersecreted GH (38%) and those whose GH secretion was reduced (62%). After recovering 10% or more of their initial weight, the GH secretion in both groups had normalized.

The effects of GH are partly mediated by somatomedins of which the most important ones are insulin-like growth factors (IGF) 1 and 2. Although somatomedins are secreted locally by several tissues, the plasma IGF-1 content mostly originates from the liver and kidneys. IGF-1 stimulates aminoacid transport, protein synthesis and body growth (Thissen et al., 1994). In patients with eating disorders, IGF-1 appears to be a biochemical marker of malnutrition, and a sensitive index of nutritional repletion (Caregaro et al., 2001). A stepwise increase in the IGF-1 values related to weight gain in anorectic patients was reported by Hill et al. (1993).

Leptin is syntetized in adipose tissue, but it regulates food intake via the hypothalamus. Leptin levels correlate with the amount of fat stores and changes in energy balance as a result of fasting (Ahima et al., 2000). Leptin levels are severely reduced in AN patients, but a significant rise already occurs after partial weight recovery (Grinspoon et al., 1996; Casanueva et al., 1997).

1.5.2. The GH-IGF-1 axis, leptin and sleep

GHRH promotes non-REM sleep in both animals and humans (Obal et al., 1988; Steiger et al., 1992). GHRH enhances both non-REM sleep duration and its intensity, as measured by slow-wave activity on the sleep EEG. The inhibition of GHRH through negative feedbacks in the somatotropic axis inhibits non-REM sleep (Obal et al., 2001). In human studies, systemic injections of somatostatin failed to alter sleep in young subjects but impaired sleep in the elderly (Frieboes et al., 1997). The main

secretion pulse of GH is closely associated with the beginning of the sleep phase when the amount of SWS is at its highest (Van Cauter et al., 1992). The delay, advance or interruption of a sleep phase will shift the main GH secretion pulse correspondingly (Goldstein et al., 1983; Van Cauter et al., 1992). Sleep deprivation also inhibits nocturnal GH secretion, while the pulses become more equally distributed through the day (Brandenberger et al., 2000). In animals, antibodies to GH have been shown to reduce non-REM sleep (Obal et al., 1997). It has been hypothesized that chronically high or low GH secretions, may alter non-REM sleep in humans (Åström, 1997).

The injection of a high dose of IGF-1 promptly inhibited sleep in rats (Obal et al., 1999). The inhibition of sleep occurs simultaneously with the inhibition of GH secretion and is attributed to the inhibition of GHRH. Low doses of IGF-1, however, increase non-REM sleep (Obal et al., 1998). In humans, the serum concentration of IGF-1 has been found to have a positive correlation with non-REM sleep quality measured as delta power (Prinz et al., 1995).

Leptin secretion has a circadian variation, with maximum levels in humans during the night, and a nadir late in the afternoon (Simon et al., 1998). In normally- fed rats, leptin administration increased the duration of SWS, but previous food deprivation negated this effect (Sinton et al., 1999).

To summarise, it can be concluded, that AN is a disorder associated with both severe hormonal disturbances, and changes in sleep architecture. Several of the hormones displaying disturbed secretion in anorectic patients have also been shown to have effects on sleep, but the correlation between the disturbed sleep and hormone secretion has not been measured in anorectic patients.

1.6. Sleep and human impulsive aggression

1.6.1. Different dimensions of impulsive aggression

As a symptom impulsive aggression cuts across a number of psychiatric disorders (Moeller, 2001), but it is commonly associated with personality disorders, in particular antisocial (ASP) and borderline (BPD) personality disorders (Eronen et al., 1996; Virkkunen et al., 1996, Goodman and New, 2000, Skodol et al., 2002). In fact, genetic, neurobiological, and diagnostic studies suggest a dimensional approach to BPD symptomatology, with impulsive aggression as one of the core dimensions of the disorder (Goodman and New, 2000; Siever et al., 2002). ASP is associated with a pervasive pattern of disregard for and the violation of the rights of others. Not surprisingly, the highest prevalence rates of ASP are found in prisons and forensic settings (American Psychiatric Association (APA), 2000). In a study by Fazel and Danesh (2002), 47% of male prisoners had ASP. ASP often co-occurs with BPD (Coid, 1993; Virkkunen et al., 1994; Hudziak, 1996; Virkkunen et al., 1996) and it has even been suggested that BPD represents a female form of male-predominant ASP (Gunderson and Zanarini, 1987). The comorbidity of BPD with ASP increases the likelihood of suicide attempts (Soloff et al., 1994).

ASP is always preceded by conduct disorder (CD) before the age of 15 (APA, 2000). The essential feature of CD is a repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated (APA, 2000). Impulsivity has been found to be the best predictor of conduct problems (Vitacco and Rogers, 2001) and impulsivity together with emotional lability may increase the likelihood of CD progressing to adult antisocial behaviour (McKay and Halperin, 2001). A strong relationship between adolescent suicide and the presence of CD problems, especially in coexistence with depression and alcohol abuse, has been reported in a study based on a Finnish nationwide population (Marttunen et al., 1991).

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood (Szatmari, 1992). The combined type of ADHD fulfills both the criteria for attention deficit as well as for hyperactivity and impulsiveness, whereas the subtypes (predominantly inattentive and predominantly hyperactive and impulsive type) do not fulfill the criteria for both symptom dimensions (APA, 1994). Prospective longitudinal studies have showed that part of the childhood onset ADHD symptoms persists in nearly half of the subjects until adolescence or early adulthood and that ADHD is a risk factor for conduct disorder, ASP and substance abuse (Gittelman et al., 1985; Mannuzza et al., 1993).

It has been argued that many individuals with personality disorders display a clinically significant impulsive-aggressive behaviour, which cannot be specifically identified by using axis II personality disorder diagnoses (Coccaro et al., 1998). In these cases, it would be better to use the diagnosis of intermittent explosive disorder (IED), which may best be regarded as a categorical expression of recurrent, problematic impulsive and aggressive behaviour (Coccaro, 2000). The essential core features of IED are: 1) the occurrence of discrete episodes of failure to resist aggressive impulses that result in serious assaultative acts or the destruction of property and 2) the degree of aggressiveness expressed during an episode is grossly out of proportion to any provocation. Besides in the research purposes, the diagnosis can also be placed to individuals with ASP and BPD in cases where impulsive aggression has specific clinical relevance (APA, 2000).

1.6.2. Testosterone and aggression

The relationship between testosterone and human aggression has been well established in many studies. High concentrations of serum testosterone have been shown to be associated with both ASP (Virkkunen et al., 1994) and severe CD (Brooks and Reddon, 1996). In a study by Stalenheim et al. (1998) serum levels of total testosterone were related to both ASP and type II alcoholism. In the study by Räsänen et al. (1999), personality-disordered criminals with multiple offences had higher serum testosterone levels than criminals with schizophrenia or healthy controls. Antisocial behaviour has been shown to be present in both rapists and child molesters and to be positively related to salivary testosterone concentrations (Aromäki et al., 2002).

1.6.3. Sleep in borderline personality disorder

BPD co-occurs with several axis I and axis II diagnoses (Cloninger and Svrakic, 2000). The problem in most of the PSG studies in BPD is that this existence of a concomitant disorder is not taken into account (De la Fuente et al., 2001). Only four studies have clearly considered the existence of additional psychiatric diagnoses in their BPD patients. Akiskal et al. (1985) found reduced REM latency in both patients with major depression but no BPD comorbidity and patients with BPD but no major depression comorbidity compared with healthy controls. Reduced REM latency compared with controls has also been reported in a study by Battaglia et al.(1993). In a study by Benson et al. (1990), non-affective BPD patients had less total sleep, more S1 sleep and less S4 sleep compared with normal controls. In the study by De La Fuente et al. (2001), BPD patients had shorter total sleep time, longer sleep onset latency and a greater percentage of wakefulness than healthy controls. They also had a longer duration of REM sleep, and less S3, S4 and SWS, but there was no difference in REM latency.

1.6.4. Sleep in conduct disorder

Only one PSG study of conduct disorder has been published. It was conducted by Coble et al.(1984). The subjects in the study were pre-adolescent boys in a psychiatric hospital. The age range was 8–13 years (10.9 years, SD 1.4). All the subjects had a normal IQ and none suffered from any demonstrable medical, organic, or neurological disorder. Standard clinical waking EEGs were normal in all cases. The primary diagnosis of CD was made after a comprehensive pediatric, neurological, psychiatric, psychological, and educational evaluation using the DSM III diagnostic criteria. The boys had not taken any medication. Seventeen normal, healthy, age-matched boys served as controls. The only difference between the groups was the higher number of delta waves found in boys with CD compared with controls. As the writers commented, the study was preliminary, but it did, however, suggest that an abnormality in the expression of SWS may be present in at least some of the children with CD.

1.6.5. Diurnal activity rhythm disturbance in intermittent explosive disorder

In a study by Virkkunen et al. (1994), 20 alcoholic, impulsive offenders with IED were studied in a forensic psychiatry ward using a wrist actigraph, which permitted continuous recordings of activity for a period of 10 days. The subjects had indistinguishable day and night activity counts, a striking difference from impulsive offenders with ASP, non-impulsive offenders and healthy volunteers. The result demonstrated a profound diurnal activity rhythm disturbance associated with IED. There are no published PSG studies in this diagnosis group.

1.6.6. The low-arousal theory

Several studies have found abnormalities in the waking EEG of antisocial persons. In a review of 1500 criminals, the most prominent form of waking EEG abnormality was the presence of theta and delta activity (Ellingson, 1954). In a study of severely aggressive individuals, the abnormality in waking EEG was localised to the temporal

lobes of the cerebral hemispheres. Within the group, the temporal abnormality was more severe in the highly aggressive subjects than the less aggressive ones (Hill, 1952). Among children with severe behavior problems including poor impulse control and inadequate socialization, the most frequent forms of waking EEG abnormality also included temporal theta and delta activity (Bayrakal, 1965). Forssman and Frey (1953) reported that antisocial boys with behaviour problems had difficulties in maintaining normal arousal levels during the waking EEG study.

These cortical findings as well as some autonomic findings, prompted Hare (1970) to formulate the low-arousal theory, which accounted for many aspects of the behaviour of antisocial persons, including impulsivity, aggressiveness, and the desire for immediate gratification. Hare suggested that such person has a pathologically low level of autonomic and cortical arousal; that he is hyporeactive compared with the normal individual, and consequently exists in a chronic state of "stimulus-hunger". Since the antisocial individual is under-reactive to stimuli, which would be stressful, exciting, or frightening to normal persons, he requires a greater variety and intensity of sensory inputs to increase his arousal level to the optimum level (Mawson and Mawson, 1977).

The low-arousal theory also builds a hypothetical link between waking EEG abnormalities and REM sleep deficits in antisocial personality disorder. According to this theory, the neuronal excitation of REM sleep in the second half of the night-time sleep may serve to maintain the central nervous system at optimal levels during waking. Antisocial persons with REM deficiency lack this nocturnal neuronal excitation and they may have to make up for it by obtaining massive amounts of sensory stimulation during the day (Hare, 1970).

The only published PSG study of antisocial criminals was conducted in order to clarify the role of REM sleep in this disorder (Salley and Khanna, 1980). No significant differences in sleep parameters, including REM sleep, were observed between the cases and the controls. However, in the study, the Rorschach content scales were used to define the caseness, and as the writers commented, another method of diagnosing could have resulted in a different outcome.

1.6.7. Neuroimaging and functional studies of brain activity predict abnormal sleep in antisocial personality disorder

Whereas earlier studies were generally more qualitative, waking EEG technology has become increasingly more advanced, allowing for detailed quantitative computerized analysis in place of clinical visual inspection (Gatzke-Kopp et al., 2001). The results of studies of these types of studies have particularly indicated temporal and frontal abnormalities in violent subjects (Convit et al., 1991; Wong et al., 1994). In a waking EEG study of a forensic population (Gatzke-Kopp et al., 2001), significant increases in slow-wave activity were found in the temporal lobes of subjects charged with either murder or manslaughter. Unfortunately, the authors did not specify how many of the violent offenders had ASP.

It is problematic to extrapolate the findings from waking EEGs to PSGs. In a study of healthy volunteers, relationships between the spectral characteristics of the waking and sleeping EEG within an individual were explored (Ehlers et al., 1998). Spectral profiles in the delta, theta, alpha and beta frequency bands of a subject's waking EEG were found to be highly correlated with their sleep EEG. These significant correlations between waking and sleep EEG made the writers suggest that the spectral signature of an individual's EEG may be found across sleep/wake states. Finelli et al. (2000) investigated the relationship between markers of sleep homeostasis during waking and sleep. The EEGs of eight young males were recorded intermittently during a 40-h wakefullness episode, as well as during baseline and recovery sleep. In the course of extended wakefulness, the spectral power of the EEG in the theta band (5–8 Hz) increased. In non-REM sleep, slow-wave activity (0.75–4.5 Hz) was enhanced on the recovery night relative to baseline. A comparison of individual records revealed a positive correlation between the rate of increase in theta activity during wakefullness and the increase in slow-wave activity in the first non-REM sleep episode. A topographic analysis showed that both effects were most intensive in frontal areas. From the results, the authors suggested that theta activity in wakefulness and slow-wave activity in sleep might be markers of a common homeostatic process. It is possible to assume, in the light of the previous two studies, that daytime EEG abnormalities measured in violent subjects could also be a marker of sleep abnormalities.

The prefrontal cortex (PFC) plays a key role in the regulation of anger and violence. Recent brain imaging studies propose a link between ASP and both structural and functional disturbances in the PFC. A reduction in prefrontal grey matter volume in the ASPs compared with controls in magnetic resonance imaging (MRI) was first demonstrated by Raine et al. (2000). In single photon emission tomography (SPET), a reduction in prefrontal cerebral blood flow (CBF) in subjects with impulsive violent crimes has been reported (Amen et al., 1996; Söderström et al., 2000). PFC also plays a role in maintaining of wakefulness and non-specific arousal (Horne 1993; Dahl 1996) and profound changes in brain metabolic activity in sleep-wake transitions have been shown to take place in frontal areas (Maquet et al., 1997; Balkin et al., 2002). It is possible to assume that the PFC deficit among the ASPs would also be reflected to their sleep.

1.7. Sleep and alcohol

1.7.1. Sleep in intoxicated non-alcoholics

Acute alcohol ingestion often has a transient sedative effect, especially in sleepy or anxious individuals. It is probably the most frequently used sleeping aid in the general population (Gillin and Drummond, 2000). In a survey of 18- to 45-year-olds in the general population, 13 % reported using alcohol during the previous year in order to fall asleep; an additional 5 % of the population used both alcohol and a hypnotic in order to sleep (Johnson et al., 1998). When given to normal controls shortly before bedtime, alcohol tends to shorten sleep latency and increase NREM sleep and to reduce REM sleep (Yules et al., 1967). In a study by Van et al. (1995) the effects of the ingestion of 0.64 g/kg alcohol on the structure of nap were compared with those of a non-alcoholic drink in eight young male subjects napping between 2 pm and 3

pm. While not affecting total nap-sleep duration, alcohol significantly increased the time in S4 sleep, primarily at the expense of the time spent in S2. Although alcohol increases sleep at the beginning of the night, it worsens it at the end of the night, when the individual is likely to be in the withdrawal state. The consequence is shallow, disrupted sleep with increased REM sleep, dream recall or lively nightmares (Gillin and Drummond, 2000).

1.7.2. Sleep in alcoholics

Cloninger et al. (1981) proposed two different kinds of alcoholism. Type 1 alcoholism is characterized by a late onset, more evidence of psychological dependence than of physical dependence, and the presence of guilt feelings concerning the use of alcohol, where as type 2 alcoholism is characterized by onset at early age, the spontaneous seeking of alcohol for consumption, and a socially disruptive set of behaviours when the person is intoxicated. Patients with type 2 alcoholism have usually been excluded from sleep studies, so the information from sleep architecture in alcoholism comes from studies of type 1 patients. The typical abnormalities seen in the sleep architecture of alcoholics are increased sleep latency, poor SE, and reduced TST, SWS and REM sleep (Benca et al., 1992). However, some tolerance develops to REM-suppressing effects of alcohol (Gillin and Drummond, 2000). Alcohol-dependent patients have been reported to have lower levels of SWS power than normal controls (Lands, 1999).

1.7.3. Sleep during recovery and abstinence

Disturbances in sleep continuity, delayed sleep onset, increased S1 sleep, reduced SWS and REM sleep abnormalities have been reported after withdrawal (Williams et al., 1981; Gillin et al., 1990; Gann et al., 2001). Mossberg et al. postulated that sleep difficulties after acute withdrawal will last approximately four to eight weeks (Mossberg et al., 1985). In a longitudinal study of alcoholic patients who were initially evaluated after an average of 32 days of sobriety, patients who relapsed at an average of five months differed in both subjective and objective sleep measures from those who remained sober. After controlling for a variety of measures, polysomnographic sleep latency was the best predictor of relapse (Brower et al., 1998). In a study by Adamson et al (1973), even after one or two years of abstinence, the sleep records of alcoholics had partly normalized, but the percentage of S4 remained at lowered levels.

2. AIMS OF THE STUDY

In this work, sleep macro- and micro-structure are studied in mental disorders (anorexia nervosa and antisocial personality disorder) and during medication (olanzapine).
The aims of the present research, study by study, were:

I. To characterize the relationships between malnutrition, PSG, power spectrum of sleep, and the hormones associated with malnutrition in patients with anorexia nervosa before and after weight gain. The hypothesis was that the levels of growth hormone axis hormones and leptin would be associated with sleep alterations in these patients.

II. To characterize the sleep of habitually violent offenders with antisocial personality disorder.

III. To characterize the relationships between different categorical diagnoses describing impulsive aggression, testosterone and sleep.

IV. To study the effects of a single dose of olanzapine on sleep and its EEG spectral power properties in healthy subjects. The hypothesis was that olanzapine would promote sleep, possibly due to its affinity to 5-HT2 receptors, and that the response might be different in women and men.

3. SUBJECTS AND METHODS

3.1. Subjects and study design

I. GH-IGF-1 axis, leptin and sleep in anorexia nervosa patients

The subjects for the study were 11 females meeting the DSM IV criteria for restricting type anorexia nervosa (APA, 1994). Diagnoses were made by the same senior psychiatrist using the SCID interview for DSM IV axis I disorders (First et al., 1996). The age range was 17–28 years, mean ± SEM 19.7 ± 1.1 years. They were hospitalised, and sleep examinations were performed on an open ward after the first week of admission. The patients had no comorbid somatic disorders, assessed by the consultant internist. The Montgomery- Åsberg Depression Rating Scale (MADRS) was used to evaluate the degree of depression. All the subjects were drug free for at least four weeks prior to the investigation. They did not smoke. The BMIs ranged between 11.0 and 14.0 kg / m^2 (mean ± SEM 13.3 ± 0.3 kg/m^2) reflecting a severe state of starvation. The mean duration of AN was 2.2 ± 0.6 years.

Patients stayed on the ward for several weeks (mean ± SEM 65.7 ± 6.4 days). During the treatment programme, patients received a standard hospital diet. Nutritional support was not given intravenously or enterally through a nasogastric tube at any phase of the treatment. The patients‘ dietary intake was progressively increased to produce a weight gain of 0.5–1.5 kg/week. Four patients started to use psychotropic medicine (neuroleptics or antidepressants) during the treatment period, and two patients left the hospital without the doctor’s permission. The study group thus consisted of five drug-free females (mean age ± SEM 21.2 ± 1.8 years) during the sleep examination after the weight gain. The BMIs of these five patients varied between 13.0 and 13.8 kg/m^2 (mean ± SEM 13.5 ± 0.2 kg/m^2) during the first sleep examination and between 15.0 and 16.0 kg/m^2 (mean ± SEM 15.6 ± 0.2 kg/m^2) during the second.

The eleven normal-weight (mean BMI ± SEM 21.4 ± 0.5 kg / m^2) controls consisted of hospital staff and students. They were gender- and age-matched (mean ± SEM 20.9 ± 0.8 years) and healthy without a history of somatic, psychiatric or neurological disorders or substance abuse. As part of a psychiatric examination, the SCID non-patient version (Spitzer et al., 1990) was filled in. The Eating Disorder Inventory (EDI) was filled in by each control and it showed no signs of an eating disorder at that time. In the interview each control described her eating habits as normal. Blood tests (including blood count, serum amylase, thyroid function, kidney and liver function) and electrocardiograms were normal. Controls were told to avoid alcohol, drugs or medication two weeks prior to the sleep examinations. Two of the controls smoked; the consumption was approximately three cigarettes a day.

The regularity of sleep-wake rhythm was assessed in both anorectics and healthy controls using sleep diaries and actigraphy for one week during the experiment period. For the sleep examinations, the controls entered the hospital at 4 pm, and the electrodes were attached between 4.30 pm and 5.30 pm. The controls slept in the guest room of the hospital while anorectics slept on the ward. Both groups were advised to continue their normal activities after the attachment of the recording elec-

trodes, and start the EEG recording when they felt sleepy. Both patients and controls were allowed to sleep as long as they wanted. The sleep recordings were made on two consecutive nights. The first night was the adaptation night and only the second night was considered for the study. The blood samples for hormone measurements were taken at 8 am after the sleep recordings.

II. Sleep among habitually violent offenders with antisocial personality disorder

The subjects for the study were 19 males (age range 18-49 years, mean ± SEM 30.7 ± 2.58 years) with a history of recurrent violent acts. They were recruited from a forensic psychiatric examination. All of them were charged with violent offences (murder, manslaughter, attempted murder or manslaughter, assault). They all met the DSM IV criteria for ASP (APA, 1994). Diagnoses were made by the same senior forensic psychiatrist using the SCID interview for DSM IV axis I and II disorders (First et al., 1996; First et al., 1997). The comorbid diagnoses are listed in **Table 1.** Subjects with psychiatric disorders known significantly to affect sleep, including psychosis, dementia or severe depression, were excluded (n = 4). The subjects were otherwise healthy, but five of them had either chronic hepatitis B or hepatitis C. The BMIs varied between 19.1 kg/m^2 and 30.6 kg/m^2 (24.4 kg/m^2, SEM 0.92). Sixteen of them had a history of alcoholism; their average age when they started to use alcohol was 13 years. Because they had been in prison before the psychiatric evaluation, they had an abstinence period of several months (mean ± SEM 4.4 ± 0.41 months). In the laboratory tests, S-GT varied between 15-68 U/L (reference values 10–60 U/L) and S-CDT between 9–20 U/L (reference values < 20 U/L). Urine screening for illicit drugs was performed just before the sleep examination and was negative in all cases. Sixteen of them smoked; the consumption was approximately 20 cigarettes a day. Brain MRI (1.5 T) disclosed no abnormality. The waking EEG was normal in 15 cases, while four subjects had a mild slowing of EEG background activity. The average IQ was low normal (mean ± SEM 90.5 ± 3.06). The mean duration of formal education was 8.7 years. The subjects stopped using medication two weeks prior to the sleep examinations.

Eleven controls were gender and age matched (age range 20-52, mean ± SEM 32.5 ± 3.44 years) as well as weight matched (mean BMI ± SEM 25.9 ± 1.22 kg/m^2) and healthy without history of somatic, psychiatric or neurological disorders or substance abuse. As part of a psychiatric examination, the SCID non- patient version (Spitzer et al., 1990) was filled in. To exclude structural brain abnormalities, brain MRI (1.5 T) was performed, and, to exclude general diseases that could affect sleep, blood tests (including serum prolactin, thyroid function, kidney and liver function) and electrocardiograms were taken. Seven of them smoked; the consumption was approximately five cigarettes a day. Controls were asked to avoid alcohol, drugs or medication for two weeks prior to the sleep examinations.

The study design was similar to that in Study I.

Table 1. The comorbid DSM IV psychiatric diagnosis among 19 males with antisocial personality disorder

301.7 ANTISOCIAL PERSONALITY DISORDER

303.90	alcohol dependence	16
304.10	anxiolytic dependence	6
304.4	amphetamine dependence	5
304.30	cannabis dependence	5
301.0	paranoid personality disorder	1
301.83	borderline personality disorder	7
300.01	panic disorder without agoraphobia	1
300.21	panic disorder with agoraphobia	1
300.4	dysthymic disorder	2

III. Human impulsive aggression: a sleep research perspective

The subjects consisted of a subgroup of habitually violent offenders presented in Study II. All 16 males met the DSM IV criteria for ASP, and, in addition six of them also for BPD. Subjects with a DSM IV axis I diagnosis other than drug and alcohol dependence were excluded (n = 2), as were subjects with an axis II diagnosis other than the two above-mentioned personality disorders (n = 1). The trial records and background information, including medical, family and criminal history from childhood and adolescence to adulthood, were studied. Using these data and information from the SCID interview for DSM IV axis I and II disorders (First et al., 1996; First et al., 1997), the severity of the preceding CD and the possible diagnosis of IED were evaluated. The severity of the preceding CD was rated as mild (lying, truancy, staying out after dark without permission), moderate (stealing without confronting a victim, vandalism) or severe (forced sex, physical cruelty, use of a weapon, stealing while confronting a victim, breaking and entering) using the descriptive guidelines of DSM IV-TR (APA, 2000). The essential features of IED (the occurrence of discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property = criterion A and the degree of aggressiveness expressed during an episode is grossly out of proportion to any provocation =criterion B) were evaluated and, in cases in which both criteria were met, the diagnosis of IED was made. In the case of one subject, not enough information was available to decide whether or not he had IED. All the diagnoses were made by two senior forensic psychiatrists with no knowledge of the results of the sleep examination. The blood samples for hormone measurements were taken at 8 am after the sleep recordings. The distribution of subjects to different clinical diagnosis groups and the overlap in the distribution can be seen in **Table 2.** The subjects had alcohol abstinence of several months (mean $\pm$ SEM 4.8 $\pm$ 0.41 months). The waking EEG was normal in 13 cases, while three subjects had mild slowing of EEG background activity.

The control group consisted of the same eleven persons described in Study II.

For sleep assessment, the sleep recordings in Study II were used.

Table 2. The overlap of different diagnostic subgroups among 16 male offenders.
ASP = antisocial personality disorder, BPD = borderline personality disorder, CDs = conduct disorder type severe, CDm = conduct disorder type mild or moderate, IED+ = intermittent explosive disorder, IED- = no intermittent explosive disorder

subject	age	index crime	ASP	BPD	CDs	CDm	IED+	IED-
1	19	attempted manslaughter	×		×			
2	46	attempted manslaughter	×		×		×	
3	27	murder	×			×		×
4	18	assault	×			×	×	
5	34	attempted manslaughter	×		×		×	
6	27	attempted manslaughter	×		×			×
7	40	manslaughter	×	×		×	×	
8	45	manslaughter	×			×		×
9	39	manslaughter	×	×	×		×	
10	39	manslaughter	×	×		×		×
11	23	assault	×	×		×	×	
12	20	murder	×	×	×		×	
13	48	attempted manslaughter	×	×		×		×
14	29	manslaughter	×			×	×	
15	20	murder and attempted manslaughter	×		×		×	
16	18	attempted manslaughter	×		×		×	

IV. Effect of a single-dose of olanzapine on sleep in healthy females and males

Seventeen healthy volunteers consisting of hospital staff and students participated in the study. Four of the 17 were excluded from the study because of technical failure (one), sedative medication by chance (one), abnormally high prolactin level (one) and an acute somatic disease during the recording procedure (one). So the study comprised seven men and six women (mean age $\pm$ SEM 25.3 $\pm$ 2.1 years versus 33.2 $\pm$ 3.0 years; t (12) = –2.214, p = 0.05). The mean body weights were $\pm$ SEM 77.9 $\pm$ 2.0 kg in males and 70.8 $\pm$ 5.8 kg in females; t (12) = –1.2, p = 0.245 and the mean BMIs were $\pm$ SEM 24.9 $\pm$ 0.8 kg/m^2 in males and 25.1 $\pm$ 1.8 kg/m^2 in females; t (12) = –0.09, p = 0.932. The subjects were asked to avoid alcohol, drugs or medication for two weeks prior to the sleep examinations. Eight of them smoked; the consumption was approximately 5 cigarettes a day. As part of a psychiatric examination, the SCID non-patient version (Spitzer et al., 1990) was filled in. To exclude structural brain abnormalities, brain MRI (1.5 T) was performed. Blood tests (including serum prolactin, thyroid function, kidney and liver function) and electrocardiograms were taken in order to exclude general diseases that could affect sleep. To exclude even mild forms of neuropsychiatric disorders, neurological examinations, including Barnes scale for akathisia, and the Abnormal Involuntary Movement Scale (AIMS) and Angus-Simpson scales for extrapyramidal symptoms, were made.

The study design was similar to that in Study I, except that three recordings were made: the adaptation night, the baseline night and the night following 10 mg of olanzapine administered at 6 pm, with placebo administered for the first and second recording nights. The participants were informed that on one of the three recording nights they would be given olanzapine and in other two nights placebo. The initial dose of

olanzapine in the treatment of schizophrenia is usually 10 mg once a day (Beasley et al., 1997; Nyberg et al., 1997), and this dose was also chosen for the study.

3.1.1. Overlap of control samples

Three healthy women volunteers, who participated in Study IV also served as controls in Study I. Among the men, seven healthy volunteers, who participated in Study IV also served as controls in Studies II and III. In all, the material consisted of 25 healthy volunteers, 11 anorectics (five of them also after weight gain) and 19 prisoners.

3.2. Methods

3.2.1. Polysomnography

Sleep EEG was recorded using a mobile recording unit (Medilog 4–24 recorder, Oxford Medical Systems, UK) allowing the subjects to move freely in the hospital. EMG surface electrodes were placed beneath the chin, EOG electrodes according to Rechtschaffen-Kales standards (Rechtschaffen and Kales, 1968). During normal sleep, the theta band has occipital dominance (Werth et al., 1997; Finelli et al., 2001), indicating that the detection of changes in theta power is most sensitive from EEG derivations over this area. As we wanted to maximise the detection of theta power, an occipital derivation was chosen for recording. Right-handed persons were recorded on derivation O2-P4 and left-handed persons on derivation O1-P3, according to the 10–20 system. The sampling frequency was 50 Hz, and the signal was attenuated using a first-order 6 dB/octave filter. The low- and high- pass filter frequencies were 25 Hz and 0.25 Hz respectively. The signal was analysed with a Nightingale sleep analyzator (Judex AB, Copenhagen, Denmark). As the derivation deviates from the standard C4-A1 arrangement created by Rechtschaffen- Kales, we carefully calibrated the signal by comparing it with the signal obtained from the standard derivation C4-A1. Electrodes were attached to locations O2-P4 and C4-A1, and the signals from these channels were compared. The wave forms from both channels were similar, but the amplitude from the derivation O2-P4 was lower. The amplitude relationship (amplification 50 microV/cm on both channels) of the signal in the C4-A1 vs. O2-P4 derivation was compared in five SWS episodes from three subjects: the amplitudes of four subsequent waves per episode were measured and their relationship (C4-A1 per O2-P4) was calculated. The mean of these relationships was 2.282 ± 0.0481 / 1. Between the subjects, the range was from 2.175 ± 0.0664 / 1 to 2.420 ± 0.0905 / 1. On the basis of these results, we modified the 75 microV delta wave amplitude criterion used in the Rechtschaffen-Kales manual to 33 microV. The rest of the scoring criterion remained the same. When this modified amplitude criterion was applied to scoring of the signal from the O2-P4 derivation (three subjects) and compared with scoring obtained from the same runs from the C4-A1 derivation, a correlation of 97.8 ± 0.1 for waking, 74.9 ± 12.0 for stage 1, 93.9 ± 0.6 for stage 2, 80.1 ± 4.9 for stage 3, 88.8 ± 3.7 for stage 4 and 88.2 ± 6.3 for REM was obtained by the same scorer. For comparison, the corresponding correlations between three repeated scorings of the same file (C4-A1 derivation) by the same scorer were: waking 93.6 ± 2.0, S1 81.1 ± 6.9, S2 90.0 ± 2.6, S3 81.5 ± 7.8, S4 91.2 ± 3.0 and REM 92.3 ± 3.4. All the data for the analysis were scored by the same scorer. Data from the adaptation nights were always omitted from the analysis.

3.2.2. Spectral power analysis

The EEG-signal was analysed after Fast Fourier transformation in five frequency bins (band widths: delta: 0.5–3.5 Hz, theta: 3.5–8.0 Hz, alpha: 8.0–12.0 Hz, sigma: 12.0–14.5 Hz and beta: 14.5–25.0 Hz), separately for stages 2, 3, and 4. The spectral powers in the delta and theta bins were normalized in each recording to the total power in stages 2 + 3 + 4 to enable comparisons between different recordings for each person and recordings between persons. SWS is most prominent during the first hours of sleep, when delta power is also at its highest (Borbély, 1982). In studies I, II, and IV, the SPA was focused on this particular period and analysed 480 epochs (4 hrs) of sleep after the appearance of the first five or more consecutive epochs of stage 2 sleep onwards. In study III, both the first half and the whole night were analysed. Results are given as percentage amounts of the given frequency bin of the total power of the studied period.

We also compared the power values obtained from the two derivations in different bands. Three EEG runs with both derivations were obtained, and scored according to Rechtschaffen-Kales-criteria from the C4-A1 derivation. Spectral power was calculated for delta, theta, alpha, sigma and beta bands in stages 2 + 3 + 4 in both derivations. When compared with the C4-A1 derivation (= 100%), the power of the O2-P4 derivation was 92.9 $\pm$ 5.3 % in delta, 118.2 $\pm$ 8.5 % in theta, 129.0 $\pm$ 13.1 % in alpha, 81.3 $\pm$ 5.1 % in sigma and 93.0 $\pm$ 5.1 % in the beta band.

3.2.3. Actigraphy

A wrist-worn actigraph (the Mini Motionlogger Actigraph, Basic Version, Ambulatory Monitoring Inc., New York, USA) was used. Analyses were conducted in one-minute epochs in the zero-crossing mode, sampling rate 10 Hz, filters were either 0 or 18 (interval device code) with equal results according to the manufacturer for sleep scoring. Sleep was defined with an algorithm by Sadeh (Sadeh et al., 1994) and commercial software (Action-W, version 1.26) was used for analysis. For the sake of convenience, subjects were allowed to choose the location of the actigraph on either the dominant or non-dominant hand. This makes a comparison between the absolute amount of activity in sleep and wakefulness unreliable between individuals but gives an accurate and comparable time for transitions between wakefulness and sleep (Sadeh et al., 1994). The wrist actigraphs were used to ensure that the subjects did not take naps during the daytime.

3.2.4. Hormone assays

Leptin (I) was quantitated with a radioimmunoassay (RIA) from Linco Research Inc., St. Charles, MO, USA. The detection limit of the assay is 0.5 microg/L. Intra-assay coefficient of variation (CV) is < 5 % in the concentration range 7–25 microg/L. Inter-assay CV is < 7% in the concentration range of 5–25 microg/L. The reference values are 7.4 $\pm$ 3.7 microg/L in women and 3.8 $\pm$ 1.8 microg/L in men.

IGF-1 (I) was quantitated with RIA from Incstar, Stillwater, MN, USA. Prior to the assay, the serum was acidified, extracted with an ODS-silica column eluted with methanol, which was evaporated. After reconstitution, RIA was performed on the

residue. The detection limit of the assay is 2 nmol/L. Intra-assay CV is < 10 % in the concentration range 9–33 nmol/L. Inter-assay CV is 13% at 9 nmol/L, 10 % at 17 nmol/L and 15 % at 33 nmol/L. The reference values are 12-48 nmol/L in women and 9-46 nmol/L in men.

GH (I) was quantitated with a time-resolved immunofluorometric assay (Auto DELFIA(tm), Wallac, Turku, Finland). The assay is calibrated against the WHO 1st IRP 80/505. The detection limit is 0.03 mU/L (conversion factor 1 microg = 1 mU). Intra-assay CV is 5 % at 0.4 mU/L and 2 % in the concentration range 5–21 mU/L. Corresponding figures for total CV is 6 % and 3 %, respectively. The reference values are 0–11 mU/L.

Testosterone (III) was quantitated with a coated-tube radioimmunoassay (Spectria, Orion Diagnostica, Espoo, Finland). The detection limit of the assay is 0.1 nmol/L. Intra-assay CV is < 8 % at 1.6–27 nmol/L. Inter-assay CV is 7% at 1.2 nmol/L and about 5% in the concentration range of 4–23 nmol/L. The reference values are 10–38 nmol/L in men, and 0.9–2.8 nmol/L in women.

3.2.5. Basic Nordic Sleep Questionnaire (BNSQ)

The subject's experience of sleep quality during the past three months (II) was assessed using a standardized questionnaire developed by the Scandinavian Sleep Research Society (Partinen and Gislason, 1995). The BNSQ contains a total of 21 questions, and 15 of which have a five-point quantitative scale (min 15, max 70 points).

3.2.6. Sleep diary

Sleep diaries were used during the study period to ensure a normal sleep-wake cycle and to exclude the effect of sleep deprivation (I–IV). Participants filled in the time of retiring to bed, estimated time of falling asleep, and the time of awakening in the morning for each consecutive night, respectively.

3.2.7. Assessment scales

The Beck Depression Inventory (BDI) (Beck et al., 1961) was used to evaluate the degree of depression (II, III, IV) as well as the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) (I). The Eating Disorder Inventory (EDI) (Garner, 1991) was used to assess eating disorder symptoms (I). The Barnes Akathisia Scale (Barnes, 1989) was used to assess clinical akathisia symptoms (IV). The Abnormal Involuntary Movement Scale (AIMS) (Smith et al., 1979) and the Angus-Simpson scale (Simpson and Angus, 1970) were used to rate extrapyramidal symptoms (IV).

3.3. Statistics

I. The results for healthy controls and 11 anorectics were compared using either a t-test (normally distributed values) or the Mann-Whitney rank sum test (non-normally distributed values). The parameters in the subgroup of five anorectics before and

after weight gain were compared using a paired t-test (all values were normally distributed). The results for controls, and anorectics before and after weight gain were compared using one-way ANOVA with the post-hoc Student-Newman-Keul's test (normally distributed values) or Kruskal-Wallis ANOVA on ranks with the post-hoc Dunn's test (non-normally distributed values). Within the groups, the correlations were made using the Pearson product moment correlation (normally distributed values) or the Spearman rank order correlation (non-normally distributed values).

II. The results were compared using either a t-test (normally distributed values) or the Mann-Whitney rank sum test (non-normally distributed values). Inside the groups, the correlations were made using the Pearson product moment correlation (normally distributed values) or the Spearman rank order correlation (non-normally distributed values).

III. The results for different subgroups of subjects with impulsive aggression and healthy controls were compared using either one-way ANOVA with the post-hoc Student-Newman-Keul's method (normally distributed values) or the Kruskal-Wallis ANOVA on ranks with the post-hoc Dunn's method (non-normally distributed values). One-way analysis of covariance with age as an independent factor was performed for the following parameters: S4%, SWS%, delta power in stages 4 and 3+4, theta power in stages 4 and 3+4, and serum testosterone level measurements. When covariance should effect, the final analysis was performed using age-adjusted values.

IV. Absolute and relative durations of sleep stages and the magnitude of delta and theta power before and after the administration of olanzapine were compared using either a paired t-test (normally distributed values) or Wilcoxon signed rank test (non-normally distributed values).

3.4. Ethics

All the studies were approved by the ethics committee at the Helsinki University Hospital. Informed consent was obtained from all the participants and, in the case of one AN patient under 18 years of age, informed consent was also obtained from her parents. It was underlined that the patients (I) and prisoners (II and III) could withdraw at any time from the study period with no negative consequences for their treatment or statements to the Finnish National Board of Medico-Legal Affairs (II and III).

4. RESULTS

The results are expressed as the mean ± SEM (I–IV).

I. GH-IGF-1 axis, leptin and sleep in anorexia nervosa patients

General conditions: The mean BMI in the AN patients was significantly lower than in the controls **(Table 3. and Fig. 1.)**. During the treatment period, the mean BMI increased significantly **(Table 3. and Fig. 2.)** although anorectics still remained underweight as compared with controls (one-way ANOVA: $F(2,18) = 72.558$; $p < 0.001$, post-hoc Student-Newman-Keul's controls vs. anorectics before weight gain $q = 15.635$, $p < 0.001$; controls vs. anorectics after weight gain $q = 11.313$, $p < 0.001$). The Montgomery- Åsberg Rating Scale expressed mild depressive symptoms in all anorexia nervosa- groups, while controls were almost symptom free **(Table 3.)**.

PSG: For details of the PSG, **see Table 3., Fig. 1. and Fig. 2.** Anorectics had significantly less TST, AST and SWS than healthy controls. They also had more S1 sleep. No significant differences were observed in any REM parameters between anorectics and controls. In the subgroup of five anorectics, the SWS increased significantly after weight gain, while both S1 and S2 decreased, but there were no differences in REM sleep parameters. With refeeding, both S1% (one-way ANOVA: $F(2,18) = 5.481$; $p = 0.01$, post-hoc Student-Newman-Keul's controls vs. anorectics before weight gain $q = 4.180$, $p < 0.009$; controls vs. anorectics after weight gain $q = 0.698$, p = NS), and SWS% (one-way ANOVA: $F(2,18) = 4.303$; $p = 0.03$, post-hoc Student-Newman-Keul's controls vs. anorectics before weight gain $q = 2.803$, $p = 0.04$; controls vs. anorectics after weight gain $q = 2.029$, p = NS) normalized to the levels of healthy controls.

SPA: For details of the SPA, **see Table 3., Fig. 1. and Fig. 2.**. The relative delta power during the first four hours of sleep did not differ significantly between anorectics and healthy controls, although a tendency towards higher delta power values in deep sleep stages was observed among controls. The weight gain did not change the delta power significantly, although a tendency towards an increase after weight gain was once again observed. The theta power was significantly higher in stages 4 and 3+4 among controls. The theta power increased significantly among AN patients after weight gain in stage 3+4.

Hormone levels: Plasma GH levels did not differ significantly between the anorectics and the controls, and the weight gain did not affect the levels significantly. However, a tendency towards higher GH levels in the controls, and in the anorectics after weight gain was observed **(Table 3., Fig. 1. and Fig. 2.)**. In anorectics both IGF-1 levels and leptin levels were reduced compared with controls **(Table 3., Fig.1.)**. In a subgroup of five anorectics, both parameters increased significantly during weight gain **(Table 3., Fig. 2.)**. IGF-1 increased to the levels of controls (Kruskal-Wallis ANOVA on ranks: $H(2,18) = 8.113$; $p = 0.02$, post-hoc Dunn's method controls vs. anorectics before weight gain $Q = 2.817$, $p < 0.05$; controls vs. anorectics after weight gain $Q = 0.606$, p = NS), while leptin still remained lower than in controls (one-way ANOVA: $F(2,18) = 13.191$; $p < 0.001$ post-hoc Student-

Neuman-Keul's controls vs. anorectics before weight gain $q = 6.516$, $p < 0.001$; controls vs. anorectics after weight gain $q = 5.085$ $p = 0.002$).

In anorectics, a negative correlation was found between S1 sleep and plasma leptin levels (Spearman $r = –0.706$, $p = 0.02$). The study also showed a positive correlation between plasma leptin levels and theta power both in stage 4 (Spearman $r = 0.632$, $p = 0.04$) and in stage 3+4 (Spearman $r = 0.742$, $p = 0.01$) among patients with AN. After weight gain, a positive correlation was seen between BMI and TST (Pearson $r = 0.892$, $p = 0.04$). In healthy controls, the BMI correlated positively with SWS (Pearson $r = 0.742$, $p = 0.02$) and SWS% (Pearson $r = 0.862$, $p = 0.003$), while in anorectics this correlation was lacking.

Table 3. The results in polysomnography, power spectral analysis and hormone assays in females with anorexia nervosa and healthy controls. CO= controls, AN= eleven anorectics, AN1= five anorectics before weight gain, AN2= five anorectics after weight gain, BMI = body mass index, MADRS = Montgomery-Åsberg Depression Rating Scale, GH = growth hormone, IGF-1 = insulin-like growth factor 1, TST = total sleep time, AST = actual sleep time, SE = sleep efficiency, S1-S4 = sleep stages 1-4, SWS = slow wave sleep, REM = rapid eye movement sleep, NS= change/difference is not statistically significant, * = non-normally distributed values. Comparisons were made using a t-test (normally distributed values), Mann-Whitney rank sum test (non- normally distributed values), and paired t-test (all values normally distributed). All values expressed as mean ± SEM.

	CO n = 11	**AN** n = 11	**CO vs AN** t df = 20	p	**AN1** n = 5	**AN2** n = 5	**AN1 vs AN2** t df = 9	p
BMI	**21.4 ± 0.53**	**13.3 ± 0.30**	**13.383**	<0.001	**13.5 ± 0.20**	**15.7 ± 0.19**	**–6.248**	0.003
MADRS	1.8 ± 0.60	9.3 ± 0.98	–6.475	**<0.001**	8.0 ± 1.10	6.4 ± 0.98	1.425	NS
hormones								
GH	0.3 ± 0.10	0.2 ± 0.06	1.185	NS*	0.1 ± 0.02	0.3 ± 0.20	–1.054	NS
IGF-1	31.7 ± 2.88	23.3 ± 1.80	2.486	**0.02**	20.2 ± 1.07	25.6 ± 1.33	–3.762	**0.02**
leptin	16.3 ± 2.40	1.2 ± 0.17	6.285	**<0.001***	1.2 ± 0.16	4.5 ± 1.25	–2.676	**0.04**
polysomnography								
TST (min)	549.3 ± 19.70	479.5 ± 15.06	2.818	**0.01**	480.2 ± 22.59	454.6 ± 37.58	0.823	NS
AST (min)	532.6 ± 18.73	446.9 ± 17.41	3.354	**0.003**	453.6 ± 27.89	445.1 ± 36.23	0.244	NS
SE (%)	97.0 ± 0.51	93.1 ± 1.73	2.178	**0.04**	94.1 ± 1.85	97.9 ± 0.38	–2.369	NS
sleep latency (min)	12.2 ± 2.88	9.1 ± 1.53	0.948	NS	7.1 ± 1.76	25.9 ± 12.94	–1.363	NS
S1 (min)	17.9 ± 3.24	34.1 ± 5.49	2.546	**0.02**	27.1 ± 3.85	12.1 ± 2.26	4.064	**0.02**
S1 (%)	3.2 ± 0.56	7.6 ± 1.12	–3.476	**0.002**	5.9 ± 0.71	2.8 ± 0.61	3.117	**0.04**
S2 (min)	285.0 ± 17.03	243.5 ± 20.53	1.557	NS	255.2 ± 33.70	225.8 ± 25.66	3.081	**0.04**
S2 (%)	53.3 ± 1.93	56.5 ± 2.41	–1.067	NS	58.5 ± 3.00	50.3 ± 2.71	5.215	**0.006**
SWS (min)	113.1 ± 5.78	73.6 ± 11.49	3.070	**0.006**	88.6 ± 19.20	113.0 ± 13.20	–2.634	NS
SWS (%)	21.4 ± 1.28	15.0 ± 2.31	2.434	**0.02**	15.7 ± 2.98	25.5 ± 2.82	–5.199	**0.007**
REM latency (min)	87.2 ± 8.35	106.6 ± 12.50	–1.289	NS	120.2 ± 22.26	96.6 ± 20.22	1.028	NS
REM (min)	116.7 ± 8.67	91.8 ± 8.01	2.110	NS	86.4 ± 11.39	94.5 ± 12.62	–0.461	NS
REM (%)	21.9 ± 1.51	20.7 ± 1.77	0.509	NS	19.7 ± 3.23	21.1 ± 2.37	–0.507	NS
spectral power analysis								
thetapower %								
stage 3	6.1 ± 1.18	5.3 ± 0.86	0.481	NS	3.7 ± 0.80	4.4 ± 1.00	–1.591	NS
stage 4	9.8 ± 1.42	5.8 ± 1.15	2.166	**0.04**	8.4 ± 3.28	11.2 ± 1.79	–2.609	NS
stage 3+4	15.9 ± 0.97	11.2 ± 1.14	3.109	**0.006**	12.1 ± 1.65	15.6 ± 2.57	–2.816	**0.05**
stage 2+3+4	30.6 ± 1.59	30.2 ± 1.52	0.187	NS	28.8 ± 2.57	28.6 ± 2.60	0.148	NS
deltapower %								
stage 3	5.0 ± 0.95	5.5 ± 1.26	–0.285	NS	4.3 ± 1.42	4.1 ± 0.42	0.190	NS
stage 4	11.8 ± 1.83	8.4 ± 2.23	1.173	NS	13.0 ± 3.43	15.3 ± 2.07	–1.464	NS
stage 3+4	16.8 ± 1.33	13.9 ± 2.53	1.026	NS	17.3 ± 3.23	19.4 ± 1.77	–1.057	NS
stage 2+3+4	26.4 ± 2.13	25.0 ± 2.89	0.395	NS	29.0 ± 2.89	27.9 ± 1.98	0.486	NS

Figure 1. Results for polysomnography, spectral power analysis and hormone assays in 11 healthy controls (CON) and 11 women with anorexia nervosa (AN). Comparisons were made using either a t-test (normally distributed values) or Mann-Whitney rank sum test (non-normally distributed values). BMI = body mass index, GH = growth hormone, IGF-1 = insulin-like growth factor 1, S1 = sleep stage 1, SWS = slow wave sleep, ST = stage.
* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$

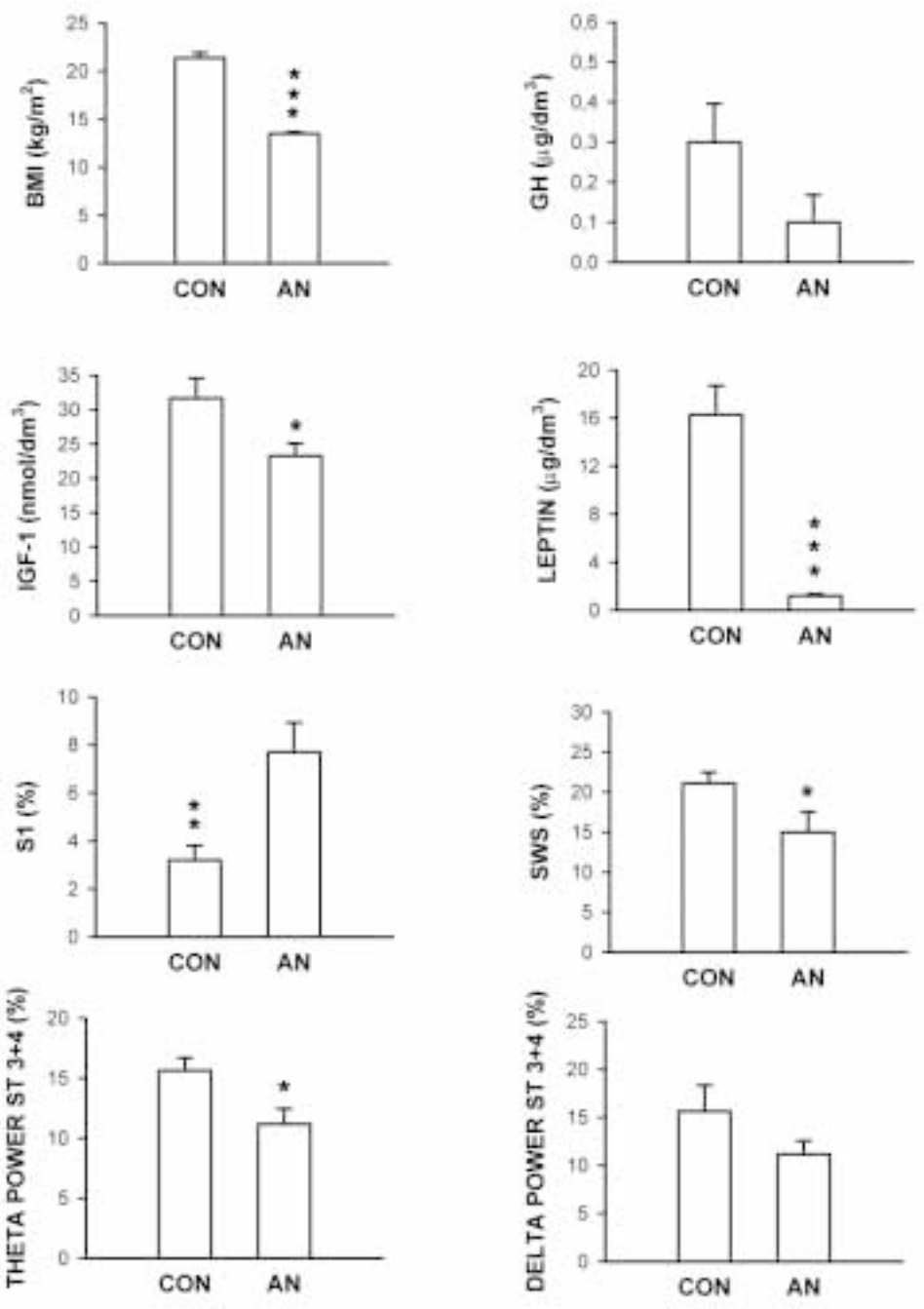
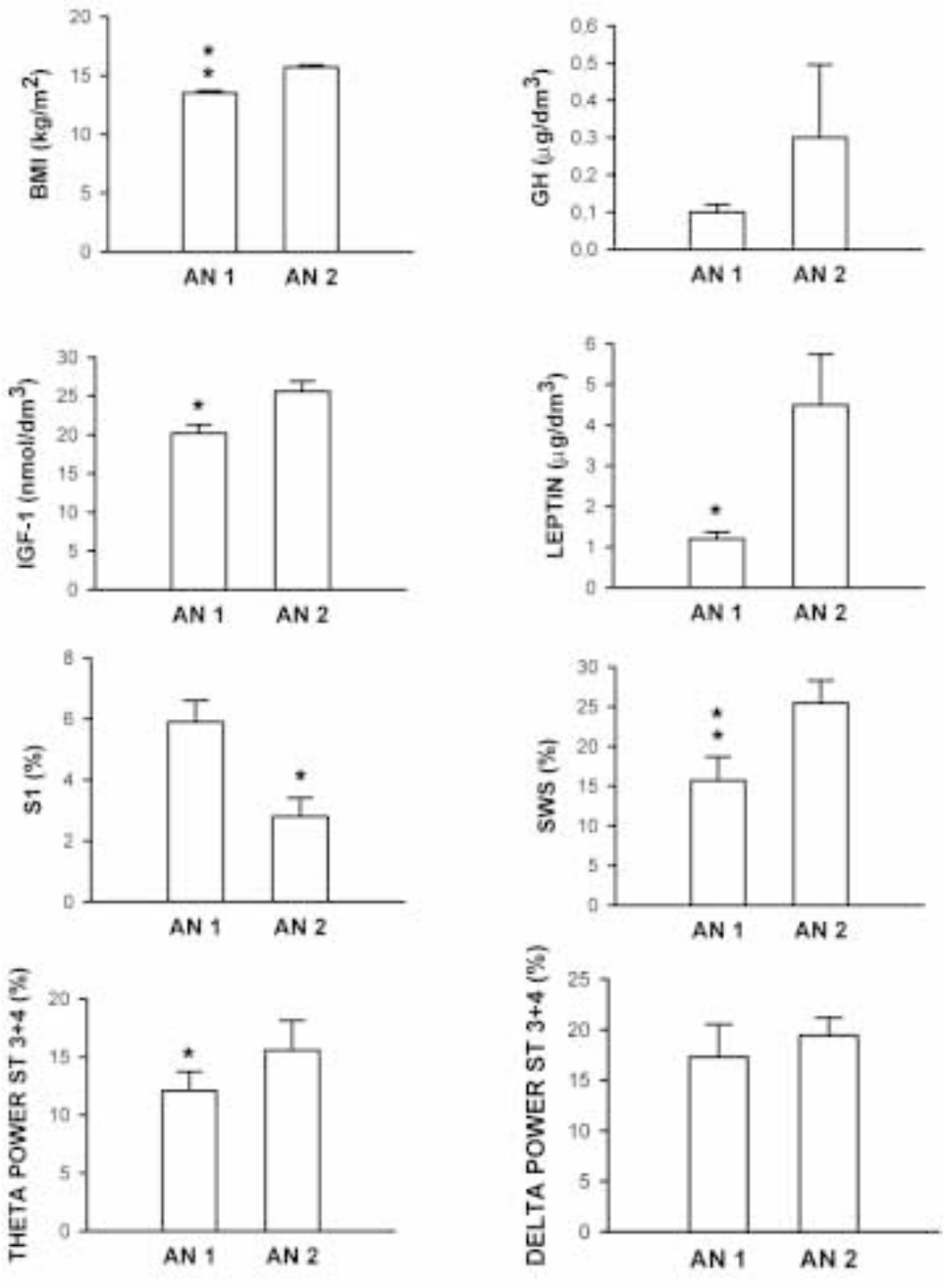


Figure 2. Results for polysomnography, spectral power analysis and hormone assays before (AN1) and after weight gain (AN2) in 5 women with anorexia nervosa. Comparisons were made using paired t-test (all values normally distributed). BMI = body mass index, GH = growth hormone, IGF-1 = insulin-like growth factor 1, S1 = sleep stage 1, SWS = slow wave sleep, ST = stage.
* = $p \leq 0.05$, ** = $p < 0.01$, *** = $p < 0.001$



II. Sleep among habitually violent offenders with antisocial personality disorder

BNSQ: The ASP individuals scored more total points on the BNSQ than the controls (35.3 ± 3.31 vs. 21.8 ± 2.27, $t(28) = -2.868$, $p = 0.008$), reflecting an impairment in subjective sleep quality. They tended to have more problems in falling asleep, they reported more awakenings during the night, they felt more sleepy in the mornings and they also reported more naps during the daytime than the controls.

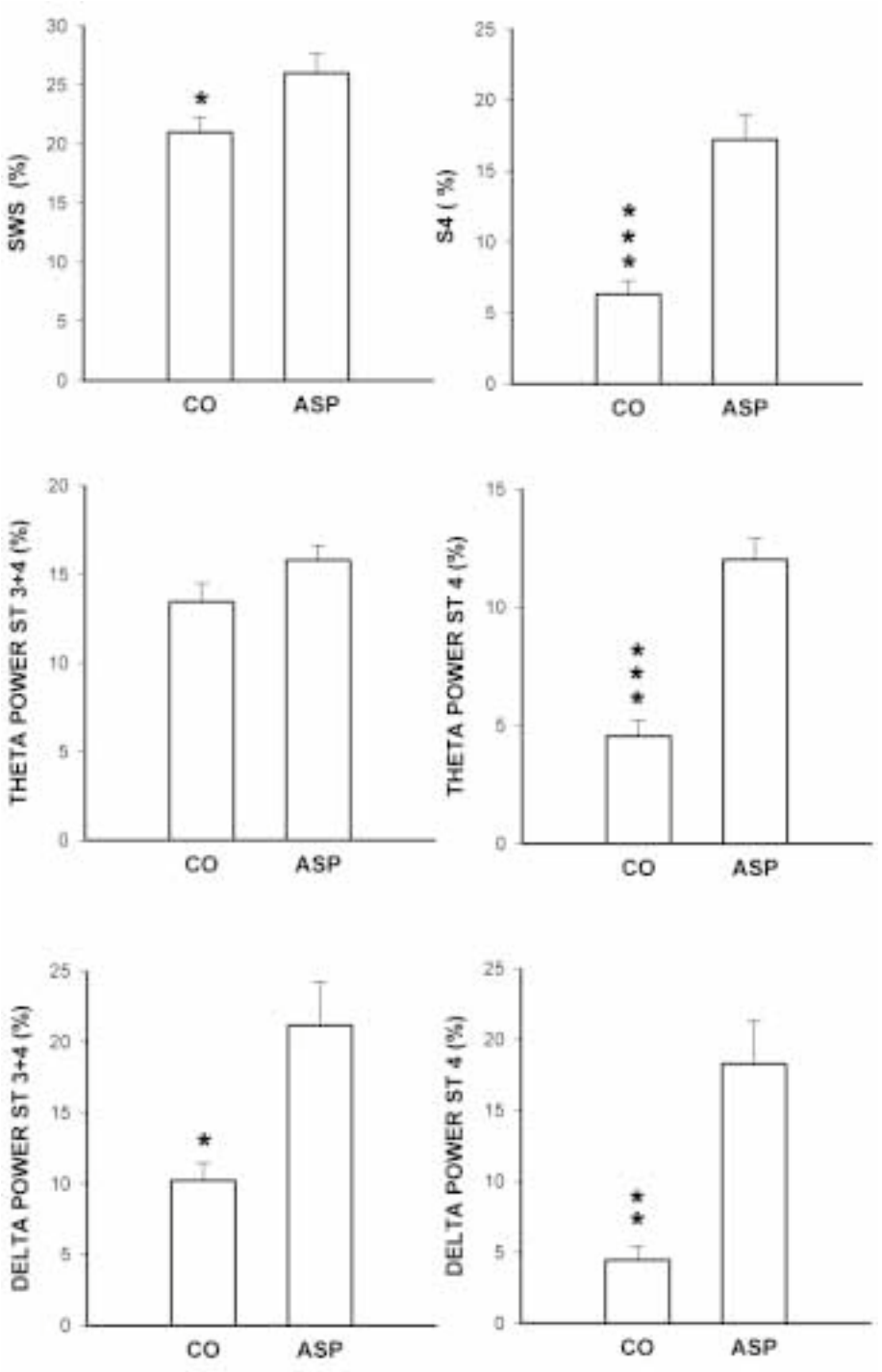
PSG*:* For details of the PSG, **see Table 4. and Fig. 3.** There was no significant difference in TST or AST between the groups. ASP individuals had significantly more awakenings during the night, and as a result, SE in ASP was lower than in the controls. No difference in sleep latency was observed. In S1, there was no significant difference between the groups, but the percentage amount of S2 was significantly higher in the controls. The percentage amount of SWS was significantly higher in ASP because the percentage of S4 in deep sleep was extremely emphasized. There were no differences in any REM sleep parameters between the groups. The negative correlation between age and SWS was found among both controls (for SWS%: Pearson $r = -0.479$, $p = 0.04$ and for S4%: Pearson $r = -0.617$, $p = 0.005$) and ASPs (for SWS % :Pearson $r = -0.635$, $p = 0.004$ and for S4%: Pearson $r = -0.606$, $p = 0.006$).

SPA: For details of the SPA, **see Table 4. and Fig. 3.** Both theta and delta power differed significantly between ASP and controls. Theta power was higher in controls in both S2 and S3, but in S4 the opposite finding was made: in this stage, theta power was much higher in ASP. Delta power was significantly higher in controls in S3, but in S4, S3+4 and S2+3+4 delta power was much higher in ASP.

Table 4. Results for polysomnography and spectral power analysis in 19 habitually violent offenders with antisocial personality disorder (ASP) and 11 healthy controls (CO). TST = total sleep time, AST = actual sleep time, SE = sleep efficiency, S1-S4 = sleep stages 1–4, SWS = slow wave sleep, REM = rapid eye movement sleep, NS = difference is not statistically significant, NP = non-normally distributed values. Comparisons were made using a t-test (normally distributed values) or Mann-Whitney rank sum test (non-normally distributed values). All values expressed as mean ± SEM.

	ASP n = 19	**CO** n = 11	tp df = 28		
polysomnography					
TST (min)	455.8 ± 17.22	461.0 ± 21.47	–0.213	NS	
AST (min)	421.1 ± 14.33	442.6 ± 22.61	–0.847	NS	
SE (%)	92.7 ± 1.22	95.7 ± 1.51	–1.526	**0.03**	NP
awakenings (n)	18.7 ± 2.17	11.7 ± 1.26	2.300	**0.03**	
sleep latency (min)	28.8 ± 7.93	18.5 ± 6.99	0.885	NS	NP
S1 (min)	26.2 ± 3.59	23.3 ± 5.38	0.454	NS	NP
S1 (%)	6.6 ± 0.83	5.3 ± 1.15	0.963	NS	NP
S2 (min)	187.5 ± 14.83	228.7 ± 11.91	–1.907	NS	
S2 (%)	45.5 ± 1.50	51.8 ± 1.33	–2.822	**0.009**	
S3 (min)	37.2 ± 3.07	63.5 ± 5.75	–4.438	**<0.001**	
S3 (%)	8.9 ± 0.79	14.6 ± 1.40	–3.879	**<0.001**	
S4 (min)	71.6 ± 7.48	24.9 ± 4.29	4.485	**<0.001**	
S4 (%)	17.2 ± 1.80	6.3 ± 0.96	4.349	**<0.001**	
SWS(min)	108.7 ± 6.74	88.4 ± 7.56	1.921	NS	
SWS (%)	26.0 ± 1.62	21.0 ± 1.31	2.141	**0.04**	
REM-latency (min)	97.3 ± 10.76	105.3 ± 16.75	–0.421	NS	NP
REM(min)	90.7 ± 4.26	98.4 ± 9.69	–0.835	NS	
REM (%)	21.6 ± 0.92	21.8 ± 1.32	–0.0885	NS	
spectral power analysis					
theta power (%)					
stage 2	11.7 ± 0.94	17.3 ± 1.17	–3.733	**<0.001**	
stage 3	3.8 ± 0.42	8.9 ± 0.75	–6.478	**<0.001**	
stage 4	12.0 ± 0.91	4.6 ± 0.67	5.742	**<0.001**	
stage 3+4	15.8 ± 0.79	13.4 ± 1.01	1.823	NS	
stage 2+3+4	27.0 ± 1.23	30.8 ± 1.59	–1.901	NS	
delta power (%)					
stage 2	7.8 ± 0.78	7.2 ± 0.79	0.473	NS	
stage 3	3.1 ± 0.37	5.8 ± 0.55	–4.097	**<0.001**	
stage 4	18.3 ± 2.99	4.5 ± 0.94	3.436	**0.002**	
stage 3+4	21.2 ± 3.02	10.2 ± 1.24	2.663	**0.01**	
stage 2+3+4	29.0 ± 3.15	17.4 ± 1.79	2.636	**0.01**	

Figure 3. Results for polysomnography and spectral power analysis in 19 antisocial violent offenders (ASP) and 11 controls (CO). Comparisons were made using a t-test (all values normally distributed). SWS = slow wave sleep, S4 = sleep stage 4, ST = stage.
* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$



III. Human impulsive aggression: a sleep research perspective

Antisocial vs. antisocial with comorbid borderline personality disorders:

General: There was no significant difference in **age** between the subject groups and healthy volunteers (antisocials 28.1 ± 3.40 years vs. antisocials with BPD comorbidity 34.8 ± 4.45 years vs. controls 32.5 ± 3.44 years; one-way ANOVA: $F(2,24) = 0.793$, p = NS). The **BDI** scores expressed mild depressive symptoms in both subject groups without significant differences between groups, while the controls were almost symptom free (antisocials 10.6 ± 2.18 vs. antisocials with BPD comorbidity 12.0 ± 2.35 vs. controls 1.6 ± 0.78; one-way ANOVA: $F(2,24) = 10.789$, $p < 0.001$, post-hoc Student-Newman-Keul's antisocials vs. antisocials with BPD comorbidity $q = 0.731$, p = NS, antisocials vs. controls $q = 5.529$, $p < 0.001$, antisocials with BPD comorbidity vs. controls $q = 5.503$, $p = 0.002$).

Polysomnography: For details of the polysomnography, see **Table 5. and Fig. 4.** Antisocials with BPD comorbidity had significantly more awakenings during the night, and, as a result, SE in this subgroup was significantly lower compared with both the ASP-group and controls. Both subgroups had significantly higher absolute and percentage amounts of S4 sleep compared with controls but there were no statistically-significant differences between subgroups. The absolute and percentage amounts of S3 sleep were lower in both subgroups compared with controls but again there was no statistically- significant difference between subgroups.

Spectral power analysis: For details of the spectral power analysis, see **Table 6. and Fig. 4.** During the first half of the sleep period, there were no statistically-significant differences between the subgroups in theta and delta power in stages 4 and 3+4. The ASP-group had higher theta power in stage 4 and delta power in stages 4 and 3+4 compared with controls. The antisocials with BPD comorbidity had higher theta power in stage 4 compared with controls. During the whole sleep period, there were no statistically-significant differences between the subgroups. The APD-group had higher theta and delta power in stages 4 and 3+4 compared with controls. The antisocials with BPD had higher theta and delta power in stage 4 compared with controls.

Serum testosterone levels: The serum testosterone levels of "pure" antisocials were mean ± SEM 20.6 ± 2.66 nmol/L and the serum testosterone levels of antisocials with BPD comorbidity were 20.4 ± 1.74 nmol/L. There were no significant differences between the age-adjusted serum testosterone levels of antisocials without and with BPD comorbidity (mean ± SEM 21.9 ± 0.88 nmol/L vs. 19.6 ± 0.45 nmol/L; $F(1,14) = 0.664$, p = NS).

Severe conduct disorder vs. mild or moderate conduct disorder:

General: There was no significant difference in **age** between the subject groups and healthy volunteers (CD type severe 27.8 ± 3.81 years vs. CD mild/ moderate 33.5 ± 3.92 years vs. controls 32.5 ± 3.44 years; one-way ANOVA: $F(2,24) = 0.631$, p =

NS). The **BDI** scores expressed mild depressive symptoms in both subject groups without significant differences between groups, while the controls were almost symptom free (CD type severe 11.6 ± 2.60 vs. CD type mild/moderate 10.6 ± 1.98 vs. controls 1.6 ± 0.78; one-way ANOVA: $F(2,24) = 10.674$, $p < 0.001$, post-hoc Student-Newman-Keul's CD type severe vs. CD type mild/moderate $q = 0.538$, $p =$ NS, CD type severe vs. controls $q = 5.778$, $p = 0.001$, CD type mild/moderate vs. controls $q = 5.200$, $p = 0.001$).

Polysomnography: For details of the polysomnography, see **Table 5. and Fig. 4.** The subgroup with preceding type severe CD had significantly higher absolute and percentage amounts of S4 sleep and SWS but less S2 sleep compared with those subjects with only mild or moderate CD and controls. Both subgroups had lower absolute and percentage amounts of S3 sleep compared with controls, but there was no statistically- significant difference between subgroups. The group with mild or moderate CD had significantly higher absolute and percentage amounts of S4 sleep compared with controls.

Spectral power analysis: For details of the spectral power analysis, see **Table 6. and Fig.4.** During the first half of the sleep period, the subgroup with preceding type severe CD had higher theta and delta powers in stages 4 and 3+4 compared with men with mild or moderate CD and controls. The subgroup with preceding type mild or moderate CD had higher theta power in stage 4 compared to controls. During the whole sleep period, the subgroup with preceding type severe CD had higher theta and delta power in stages 4 and 3+4 compared with men with mild or moderate CD and controls. The subgroup with preceding type mild or moderate CD had higher theta and delta power in stage 4 compared with controls.

Serum testosterone levels: The serum testosterone levels of the group with preceding type severe CD were mean ± SEM 24.1 ± 1.83 nmol/L and the serum testosterone levels of the group with preceding type mild or moderate CD were16.9 ± 1.27 nmol/L. The group with preceding type severe CD had significantly higher age-adjusted serum testosterone levels than those with only mild or moderate CD (mean ± SEM 23.5 ± 0.52 nmol/L vs. 17.4 ± 0.52 nmol/L; $F(1,14) = 2.882$, $p = 0.01$).

Intermittent explosive disorder vs. no intermittent explosive disorder:

General: There was no significant difference in **age** between the subject groups and healthy volunteers (IED+ 28.5 ± 3.36 years vs. IED- 37.2 ± 4.41 years vs. controls 32.5 ± 3.44 years; one-way ANOVA: $F(2,23) = 1.106$, $p =$ NS). The **BDI** scores expressed mild depressive symptoms in both subject groups without significant differences between groups, while the controls were almost symptom free (IED+ 12.6 ± 2.00 vs. IED- 10.0 ± 2.55 vs. controls 1.6 ± 0.78; one-way ANOVA: $F(2,23) = 13.824$, $p < 0.001$, post-hoc Student-Newman-Keul's IED+ vs. IED- $q = 1.364$, $p =$ NS, IED+ vs. controls $q = 7.211$, $p < 0.001$, IED- vs. controls $q = 4.456$, $p = 0.005$).

Polysomnography: For details of the polysomnography, see **Table 5. and Fig. 4.** The only statistically- significant differences in sleep parameters between males with IED and males without this diagnosis were found in S4 sleep and in SWS, with

higher absolute and percentage amounts of S4 sleep and absolute amount of SWS in men with IED. The absolute and percentage amounts of S4 sleep and absolute amount of SWS were higher in men with IED compared with controls, while absolute and percentage amounts of S3 sleep were lower. The absolute amount of S3 sleep was significantly decreased in men without IED compared with controls.

Spectral power analysis: For details of the spectral power analysis, see **Table 6. and Fig. 4.** During the first half of the sleep period, the subgroup with IED had higher theta power in stages 4 and 3+4 and delta power in stage 4 compared with men without this diagnosis. The subgroup with IED had higher theta and delta power in stages 3 and 3+4 compared with controls. There were no statistically-significant differences between subjects without IED and controls. During the whole sleep period, the subgroup with IED had higher theta and delta power in stage 4 compared with men without the diagnosis. The subgroup with IED had higher theta power in stage 4 and delta power in stage 4 and 3+4 compared with controls. The subgroup without IED had higher theta and delta power in stage 4 compared with controls.

Serum testosterone levels: The serum testosterone levels of men with IED were mean $\pm$ SEM 21.8 $\pm$ 1.65 nmol/L and the serum testosterone levels of men without IED were 16.4 $\pm$ 2.10 nmol/L. There was a tendency towards higher age-adjusted serum testosterone levels in men with IED compared with subjects without this diagnosis, although the difference was not statistically significant (mean $\pm$ SEM 21.3 $\pm$ 0.51 nmol/L vs.17.4 $\pm$ 1.05 nmol/L; $F(1,13) = 1.567$, $p = 0.08$).

Table 5. The polysomnography parameters.
A = antisocial personality disorder, B = antisocial and borderline personality disorders CDs = conduct disorder type severe, CDm = conduct disorder type mild or moderate, IED+ = intermittent explosive disorder, IED- = no intermittent explosive disorder, CO = controls, TST = total sleep time, AST = actual sleep time, SE = sleep efficiency, S1-S4 = sleep stages 1–4, SWS = slow wave sleep, REM = rapid eye movement sleep, lat = latency, NS = difference is not statistically significant. Comparisons made using one-way ANOVA with post-hoc Student-Newman-Keul's method (normally distributed values) and Kruskal- Wallis ANOVA on ranks with post-hoc Dunn's method (non-normally distributed values). * = one-way analysis of covariance with age as an independent factor. All values expressed as mean ± SEM.

	A n = 10	**B** n = 6	**CO** n = 11	**statistics**
Polysomnography				
TST (min)	429.7 ± 24.37	500.3 ± 35.29	461.8 ± 21.47	F = 1.606, P = NS
AST (min)	396.9 ± 18.66	455.3 ± 28.09	442.6 ± 22.61	F = 1.778, P = NS
SE (%)	95.3 ± 0.86	89.3 ± 2.85	95.7 ± 1.51	**F = 3.890, P = 0.03**
				A vs. B q = 3.400, P = 0.02
				B vs. CO q = 3.705, P = 0.04
sleep lat (min)	21.4 ± 8.21	17.9 ± 5.40	18.5 ± 7.00	H = 0.877, P = NS
awakenings (n)	10.7 ± 1.65	24.7 ± 4.53	11.7 ± 1.26	**F = 9.815, P< 0.001**
				A vs. B q = 5.823, P= 0.001
				B vs. CO q = 5.489, P< 0.001
S1 (min)	23.6 ± 5.79	26.9 ± 2.12	23.3 ± 5.38	H = 2.878, P = NS
S1 (%)	6.7 ± 1.39	6.0 ± 0.64	5.3 ± 1.15	H = 1.610, P = NS
S2 (min)	176.8 ± 12.53	226.3 ± 26.54	228.7 ± 11.91	**F = 3.873, P = 0.04**
				A vs. CO q = 3.648, p = 0.042
				A vs. B q = 2.942, p = 0.048
S2 (%)	44.3 ± 1.83	49.0 ± 3.44	51.7 ± 1.33	**F = 4.194, P = 0.03**
				A vs. CO q = 4.077, P 0.02
S3 (min)	38.5 ± 3.66	36.6 ± 5.78	63.5 ± 5.74	**F = 8.916, P = 0.001**
				A vs. CO, q = 5.200, P = 0.001
				B vs. CO, q = 4.810, P = 0.006
S3 (%)	9.9 ± 1.17	7.7 ± 0.89	14.6 ± 1.40	**F = 7.144, P = 0.004**
				A vs. CO q = 3.899, P = 0.01
				B vs. CO q = 4.934, P = 0.005
S4 (min)	68.2 ± 10.34	63.8 ± 11.21	24.9 ± 4.29	**F = 8.856, P = 0.001**
				A vs. CO q = 5.528, P = 0.002
				B vs. CO q = 4.279, P = 0.006
S4 (%)	17.2 ± 2.48	14.4 ± 2.63	6.3 ± 0.96	**F = 9.107, P = 0.001***
				A vs. CO q = 3.960, P < 0.001
				B vs. CO q = 2.997, P = 0.006
SWS (min)	104.8 ± 9.93	100.3 ± 11.99	88.4 ± 7.56	F = 0.914, P = NS
SWS (%)	27.1 ± 2.38	22.1 ± 2.32	21.0 ± 1.31	F = 2.209, P = NS*
REM lat (min)	111.9 ± 8.25	83.2 ± 10.84	105.3 ± 16.75	F = 0.951, P = NS
REM (min)	86.2 ± 6.10	101.7 ± 6.70	98.4 ± 9.69	F = 0.934, P = NS
REM (%)	21.7 ± 1.18	22.7 ± 2.05	21.8 ± 1.32	F = 0.128, P = NS

	CDs n= 8	**CDm** n= 8	**CO** n=11	**statistics**
Polysomnography				
TST (min)	425.4 ± 25.90	478.0 ± 28.33	461.8 ± 21.47	F = 1.055, P = NS
AST (min)	402.9 ± 24.1	434.6 ± 23.57	442.6 ± 22.61	F = 0.773, P = NS
SE (%)	94.8 ± 1.38	91.3 ± 2.28	95.7 ± 1.51	H = 5.765, P = NS
sleep lat (min)	26.1 ± 9.67	30.9 ± 16.57	18.5 ± 7.00	F = 0.346, P = NS
awakenings (n)	14.5 ± 2.87	21.6 ± 4.01	11.7 ± 1.26	**F = 3.630, P = 0.04**
				CDm vs. CO q = 3.765, P = 0.04
S1 (min)	17.9 ± 3.21	31.9 ± 5.71	23.3 ± 5.38	F = 1.720, P = NS
S1 (%)	5.6 ± 1.07	7.4 ± 1.40	5.3 ± 1.15	F = 0.843, P = NS
S2 (min)	157.1 ± 24.65	218.8 ± 21.35	228.7 ± 11.91	**F = 4.154, P = 0.03**
				CDs vs. CDm q = 3.115, P = 0.04
				CDs vs. CO q = 0.029, P = 0.03
S2 (%)	42.6 ± 1.91	49.5 ± 2.47	51.7 ± 1.33	**F = 6.596, P = 0.005**
				CDs vs. CDm q = 3.528, P = 0.02
				CDs vs. CO q = 5.045, P = 0.004
S3 (min)	36.4 ± 5.24	39.1 ± 3.41	63.5 ± 5.75	**F = 8.968, P = 0.001**
				CDs vs. CO q = 5.289, P = 0.003
				CD m vs. CO q = 4.776, P = 0.003
S3 (%)	9.2 ± 1.55	9.0 ± 0.74	14.6 ± 1.40	**F = 6.238, P = 0.007**
				CDs vs. CO q = 4.138, P = 0.008
				CDm vs. CO q = 4.281, P = 0.02
S4 (min)	83.4 ± 9.18	49.7 ± 8.66	24.9 ± 4.29	**F = 17.409, P < 0.001**
				CDs vs. CDm q = 4.472, P = 0.004
				CDs vs. CO q = 8.345, P < 0.001
				CDm vs. CO q = 3.533, P = 0.02
S4 (%)	20.6 ± 1.91	11.6 ± 2.19	6.3 ± 0.96	**F = 19.167, P<0.001***
				CDs vs. CDm q = 3.394, P = 0.002
				CDs vs. CO q = 6.191, P< 0.001
				CDm vs. CO q = 2.567, P = 0.02
SWS (min)	119.9 ± 9.88	88.6 ± 7.75	88.46 ± 7.56	**F = 4.397, P = 0.02**
				CDs vs. CDm q = 3.524, P = 0.02
				CDs vs. CO q = 3.813, P = 0.03
SWS (%)	29.8 ± 1.93	20.6 ± 2.00	21.0 ± 1.31	**F = 8.250, P = 0.002***
				CDs vs. CDm q = 3.455, P = 0.002
				CDs vs. CO q = 3.696, P = 0.001
REM lat (min)	125.7 ± 18.77	72.4 ± 11.43	105.3 ± 16.75	F = 2.404, P = NS
REM (min)	88.3 ± 7.13	95.6 ± 6.74	98.4 ± 9.69	F = 0.367, P = NS
REM (%)	21.9 ± 1.28	22.3 ± 1.72	21.8 ± 1.32	F = 0.034, P = NS

	IED+ n= 10	**IED-** n= 5	**CO** n= 11	**statistics**
polysomnography				
TST (min)	455.3 ± 21.78	458.5 ± 47.77	461.8 ± 21.47	F = 0.018, P = NS
AST (min)	428.7 ± 21.41	409.2 ± 33.55	442.6 ± 22.61	F = 0.376, P = NS
SE (%)	94.0 ± 1.01	90.5 ± 3.87	95.7 ± 1.51	H = 4.084, P = NS
sleep lat (min)	33.1 ± 13.59	11.0 ± 5.32	18.5 ± 7.00	H = 3.109, P = NS
awakenings (n)	17.8 ± 1.84	21.0 ± 7.31	11.7 ± 1.26	H = 4.752, P = NS
S1 (min)	21.1 ± 2.49	36.2 ± 8.59	23.3 ± 5.38	F = 1.779, P = NS
S1 (%)	5.8 ± 0.74	8.8 ± 2.03	5.3 ± 1.15	H = 4.479, P = NS
S2 (min)	195.9 ± 18.47	172.5 ± 45.94	228.7 ± 11.91	F = 1.595, P = NS
S2 (%)	45.0 ± 2.50	47.2 ± 2.66	51.7 ± 1.33	F = 3.159, P = NS
S3 (min)	36.3 ± 3.95	42.0 ± 5.74	63.5 ± 5.75	**F = 8.445, P = 0.002**
				IED+ vs. CO q = 5.605, P = 0.002
				IED- vs. CO q = 0.019, P = 0.02
S3 (%)	8.3 ± 0.75	10.7 ± 2.19	14.6 ± 1.40	**F = 6.658, P = 0.005**
				IED+ vs. CO q = 5.122, P = 0.004
S4 (min)	79.4 ± 8.50	38.8 ± 8.26	24.9 ± 4.29	**F = 18.784, P < 0.001**
				IED+ vs. IED- q = 5.057, P = 0.002
				IED+ vs. CO q = 8.509, P < 0.001
S4 (%)	18.9 ± 2.07	9.6 ± 2.22	6.3 ± 0.96	**F = 15.131, P< 0.001***
				IED+ vs. IED- q = 2.822, P = 0.01
				IED+ vs. CO q = 5.484, P< 0.001
SWS (min)	115.7 ± 8.95	80.6 ± 8.37	88.4 ± 7.56	**F = 4.345, P = 0.03**
				IED+ vs. IED- q = 3.555, P = 0.05
				IED+ vs. CO q = 3.464, P = 0.02
SWS (%)	27.2 ± 2.02	20.4 ± 3.36	21.0 ± 1.31	F = 2.653, P = NS*
REM lat (min)	86.6 ± 9.53	126.8 ± 35.08	105.3 ± 16.75	F = 1.006, P = NS
REM (min)	92.0 ± 4.52	96.6 ± 12.46	98.4 ± 9.69	F = 0.165, P = NS
REM (%)	21.7 ± 1.54	23.4 ± 2.39	21.8 ± 1.32	F = 0.317, P = NS

Table 6. The percentual spectral power in relation to the total power in stages 2+3+4. A = antisocial personality disorder, B = antisocial and borderline personality disorders, CDs = conduct disorder type severe, CDm = conduct disorder type mild or moderate, IED+ = intermittent explosive disorder, IED- = no intermittent explosive disorder, CO = controls, NS = difference is not statistically significant. Comparisons made using one-way ANOVA with post-hoc Student- Newman-Keul's method (all values normally distributed) * = one-way analysis of covariance with age as an independent factor. All values expressed as mean ± SEM.

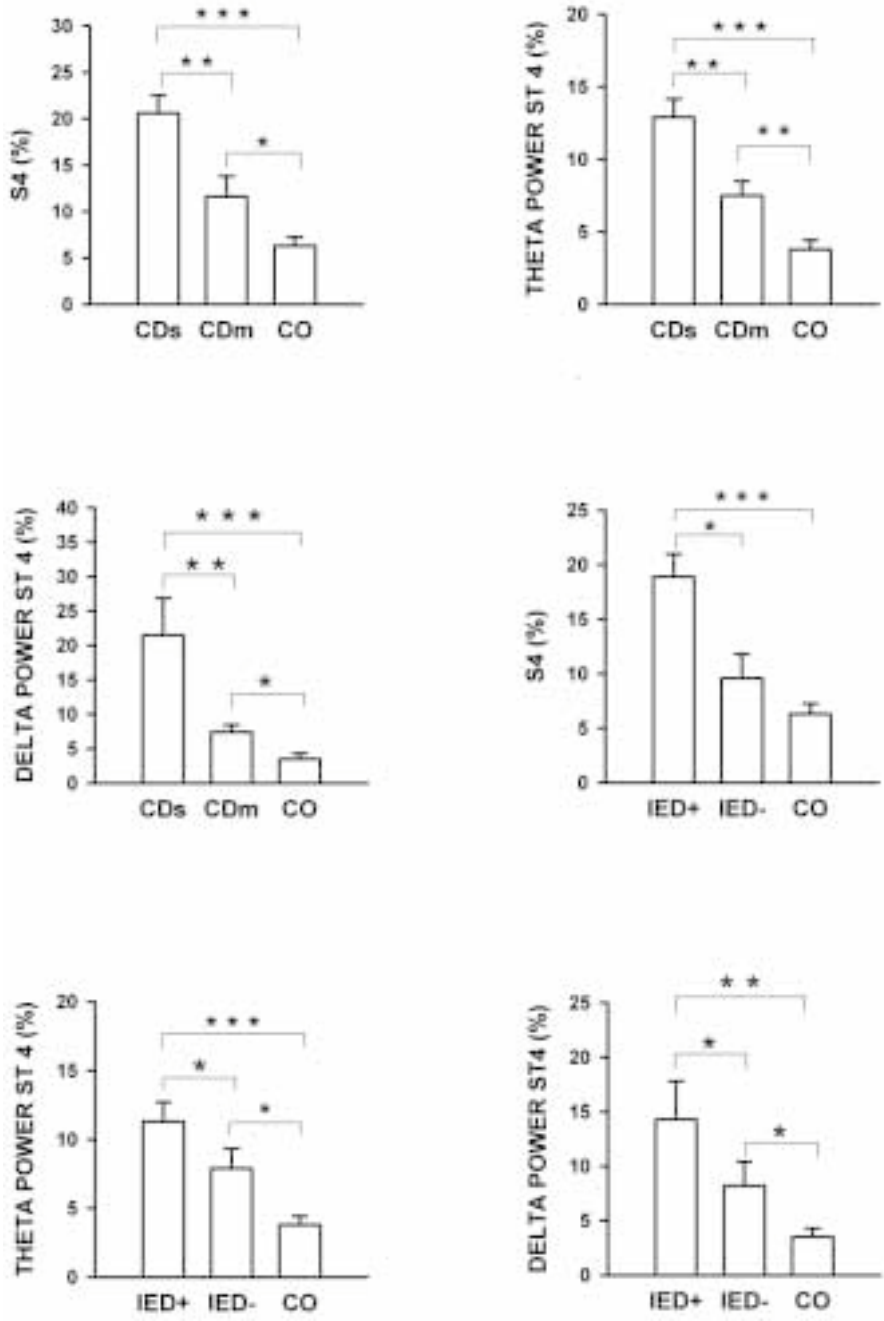
	A n = 10	**B** n = 6	**CO** n = 11	**statistics**
first half of the night				
theta power (%)				
stage 4	13.6 ± 1.17	10.8 ± 2.55	5.0 ± 0.93	**F = 11.546, P < 0.001**
				A vs. CO q = 6.679, P < 0.001
				B vs. CO q = 3.883, P = 0.01
stage 3+4	17.4 ± 0.81	14.8 ± 2.47	13.9 ± 0.88	F = 2.442, P = NS
delta power (%)				
stage 4	20.9 ± 5.03	12.4 ± 3.25	4.9 ± 1.17	**F = 5.907, P = 0.008**
				A vs. CO q = 4.861, P = 0.006
stage 3+4	24.2 ± 5.13	15.6 ± 3.21	10.9 ± 1.52	**F = 3.850, P = 0.04**
				A vs. CO q = 3.900, P = 0.03
the whole night				
theta power (%)				
stage 4	11.7 ± 1.16	7.7 ± 1.66	3.8 ± 0.63	**F = 15.267, P < 0.001***
				A vs. CO q = 5.490, P < 0.001
				B vs. CO q = 2.696, P = 0.01
stage 3+4	15.4 ± 0.88	11.3 ± 1.58	11.3 ± 0.95	**F = 4.194, P = 0.03***
				A vs. CO q = 2.739, P = 0.01
delta power (%)				
stage 4	17.7 ± 4.73	9.0 ± 2.41	3.5 ± 0.80	**F = 8.938, P = 0.001***
				A vs. CO q = 4.082, P < 0.001
				B vs. CO q = 2.594, P = 0.02
stage 3+4	21.2 ± 4.88	12.1 ± 2.51	8.3 ± 1.11	**F = 5.040, P = 0.02***
				A vs. CO q = 3.154, P = 0.004

	CDs n = 8	**CDm** n = 8	**CO** n = 11	**statistics**
first half of the night				
theta power (%)				
stage 4	15.5 ± 1.14	9.6 ± 1.56	5.0 ± 0.93	**F = 20.152, P < 0.001**
				CDs vs. CDm q = 4.706, P = 0.003
				CDs vs. CO q = 8.977, P < 0.001
				CDm vs. CO q = 3.913, P = 0.01
stage 3+4	18.8 ± 0.97	14.0 ± 1.48	13.9 ± 0.88	**F = 6.202, P = 0.007**
				CDs vs. CDm q = 4.142, P = 0.007
				CDs vs. CO q = 4.560, P = 0.01
delta power (%)				
stage 4	25.9 ± 5.44	9.6 ± 1.60	4.9 ± 1.17	**F = 13.140, P < 0.001**
				CDs vs. CDm q = 5.112, P = 0.002
				CDs vs. CO q = 7.084, P < 0.001
stage 3+4	28.9 ± 5.67	13.0 ± 1.55	10.9 ± 1.52	**F = 9.244, P = 0.001**
				CDs vs. CDm q = 4.728, P = 0.003
				CDs vs. CO q = 5.767, P = 0.001

the whole night				
theta power (%)				
stage 4	12.9 ± 1.26	7.5 ± 0.99	3.8 ± 0.63	**F = 24.204, P < 0.001***
				CDs vs. CDm q = 3.616, P = 0.002
				CDs vs. CO q = 6.951, P < 0.001
				CDm vs. CO q = 3.096, P = 0.005
stage 3+4	16.0 ± 1.0	11.8 ± 1.17	11.3 ± 0.95	**F = 4.734, P = 0.02***
				CDs vs. CDm q = 2.323, P = 0.03
				CDs vs. CO q = 2.968, P = 0.007
delta power (%)				
stage 4	21.5 ± 5.36	7.4 ± 1.05	3.5 ± 0.80	**F = 11.230, P < 0.001***
				CDs vs. CDm q = 3.986, P = 0.002
				CDs vs. CO q = 4.662, P < 0.001
				CDm vs. CO q = 2.674, P = 0.01
stage 3+4	24.7 ± 5.62	10.8 ± 1.28	8.3 ± 1.11	**F = 7.762, P = 0.003***
				CDs vs. CDm q = 2.306, P = 0.03
				CDs vs. CO q = 3.938, P < 0.001

	IED+ n = 10	**IED-** n = 5	**CO** n = 11	**statistics**
first half of the night				
theta power (%)				
stage 4	14.4 ± 1.46	9.0 ± 1.66	5.0 ± 0.93	**F = 15.745, P < 0.001**
				IED+ vs. IED- q = 3.688, P = 0.02
				IED+ vs. CO q = 7.925, P < 0.001
stage 3+4	18.1 ± 1.14	13.4 ± 1.90	13.9 ± 0.88	**F = 4.981, P = 0.02**
				IED+ vs. IED- q = 3.499, P = 0.05
				IED+ vs. CO q = 3.980, P = 0.01
delta power (%)				
stage 4	18.1 ± 3.39	9.6 ± 2.92	4.9 ± 1.17	**F = 7.879, P = 0.002**
				IED+ vs. IED- q = 2.857, P 0.05
				IED+ vs. CO q = 5.584, P = 0.002
stage 3+4	21.0 ± 3.16	13.1 ± 3.28	10.9 ± 1.52	**F = 4.731, P = 0.02**
				IED+ vs. CO q = 4.246, P = 0.02
the whole night				
theta power (%)				
stage 4	11.3 ± 1.42	7.9 ± 1.42	3.8 ± 0.63	**F = 12.700, P < 0.001***
				IED+ vs. IED- q = 2.462, P = 0.04
				IED+ vs. CO q = 4.944, P < 0.001
				IED- vs. CO q = 2.628, P = 0.02
stage 3+4	14.8 ± 1.16	12.5 ± 1.80	11.3 ± 0.95	F = 2.107, P = NS*
delta power (%)				
stage 4	14.3 ± 3.49	8.2 ± 2.23	3.5 ± 0.80	**F = 7.890, P = 0.003***
				IED+ vs. IED- q = 3.012, P = 0.02
				IED+ vs. CO q = 3.803, P = 0.001
				IED- vs. CO q = 2.393, P = 0.03
stage 3+4	17.2 ± 3.48	12.0 ± 2.95	8.3 ± 1.11	**F = 4.008, P = 0.03***
				IED+ vs. CO q = 2.751, P = 0.01

Figure 4. Results for polysomnography and spectral power analysis during the whole night in different subgroups of antisocial violent offenders (CDs = 8 males with preceding type severe conduct disorder, CDm = 8 males with preceding type mild or moderate conduct disorder, IED+ = 10 males with intermittent explosive disorder, IED- = 5 males with no intermittent explosive disorder) and 11 controls (CO). Comparisons were made using one- way ANOVA with post- hoc Student-Newman-Keul´s method (all values normally distributed). S4 = sleep stage 4, ST = stage.
* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$



IV. Effect of a single-dose of olanzapine on sleep in healthy females and males

General conditions: The study comprised seven men and six women (age 25.3 years ± 2.1 vs. 33.2 years ± 3.0; t (12) = –2.214, p = 0.05). Neither the body weights (70.8 kg ± 5.8 in females vs. 77.9 kg ± 2.0 in males; t (12)= 1.2, p = NS) nor the body mass indexes (BMI) (25.1 ± 1.8 in females vs. 24.9 ± 0.8 in males; t (12) = 0.09, p = NS) differed significantly between the sexes.

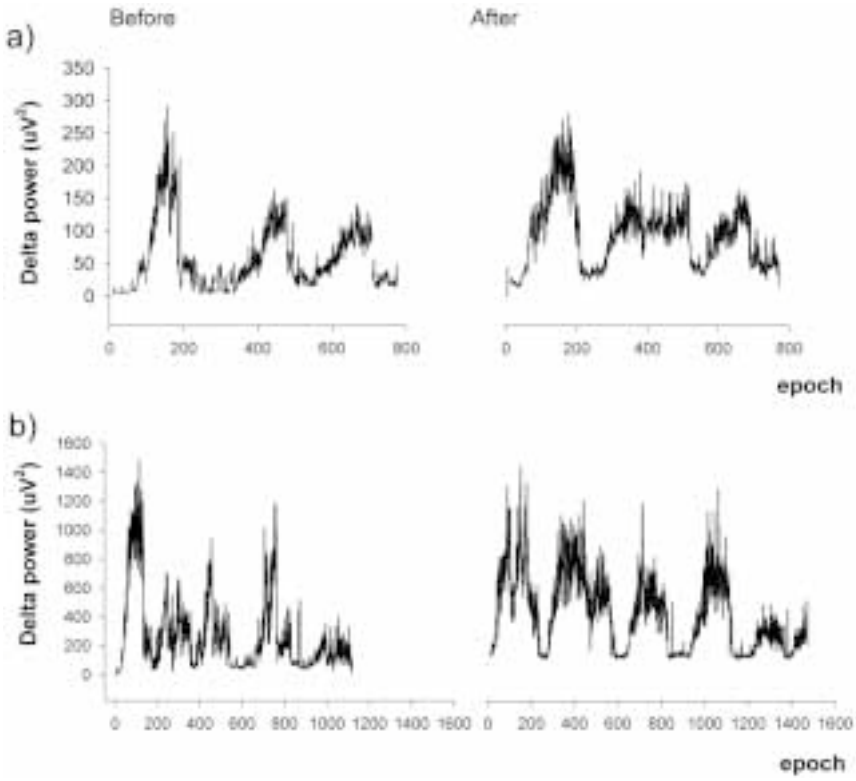
PSG: The number and structure of sleep cycles did not change after olanzapine administration. The decline in delta power both within an individual sleep bout and during successive sleep bouts across the night remained normal. After olanzapine administration, the sleep bouts appeared to be more consolidated **(Figure 5.)**. For details of the PSG, **see Table 7. and Figure 6.** Sleep latency, AST and SWS (both actual and percentage amount) was higher in both sexes, but the increases were only statistically significant in women. The same phenomenon was observed in REM latency and in total duration of REM sleep in minutes. The percentage amount of REM sleep decreased in both sexes, but the change was only significant in women.

SPA: Olanzapine slightly increased the relative delta power in stages 2 + 3+ 4 during the first four hours of sleep in both sexes, but the changes were not statistically significant (all 16.486 ± 2.193 vs. 17.788 ± 1.876; t (12) = –1.371, p= NS, men 16.657 ± 2.431 vs. 17.192 ± 2.130; t (6) = -0.461, p = NS, women 16.286 ± 4.089 vs. 18.483 ± 3.431; t (5) = -1.388, p = NS). The relative theta power in stages 2+3+4, on the other hand, increased significantly in both sexes (all 28.818 ± 1.650 vs. 33.223 ± 1.713; t (12) = -3.834, p = 0.002, men 29.467 ± 2.338 vs. 32.812 ± 2.382; t (6) = -3.477, p = 0.01, women 28.062 ± 2.509 vs. 33.703 ± 2.690; t (5) = –2.523, p = 0.05) **(Figure 6.)**.

Table 7. Results for polysomnography in 13 healthy subjects (7men and 6 women) before and after administration of 10 mg olanzapine. Comparisons were made using paired t-test (normally distributed values) or Wilcoxon signed rank test (non-normally distributed values). SE = sleep efficiency, AST = actual sleep time, S1-S4 = sleep stages 1–4, SWS = slow wave sleep, REM = rapid eye movement sleep, NS = change is not statistically significant, NP = non-normally distributed values. All values expressed as mean ± SEM.

ALL	**before**	**after**	**t (df=12)**	**p**
sleep latency (min)	316.8±12.5	224.4± 24.3	3.462	**0.005**
SE (%)	6.6± 1.0	97.3± 1.1	–0.783	NS
AST (min)	461.2 ± 23.6	585.8 ±41.7	–3.789	**0.003**
awakenings (n)	14.3 ± 1.7	13.3 ± 3.1	0.491	NS
S1 (min)	24.5 ± 5.8	16.5 ± 3.7	–1.539	NS/NP
S1 (%)	5.1 ± 1.4	2.9 ± 0.7	2.112	NS
S2 (min)	238.1 ± 13.9	296.9 ± 24.7	–3.383	**0.005**
S2 (%)	51.3 ± 1.3	50.1 ± 1.3	2.236	**0.04**
S3 (min)	66.3 ± 4.4	101.5 ± 7.2	–4.036	**0.002**
S3 (%)	14.6 ± 1.0	17.6 ± 0.8	–2.969	**0.01**
S4 (min)	30.2 ± 5.1	46.7 ± 8.3	–2.393	**0.03**
S4 (%)	6.1 ± 0.9	7.6 ± 1.1	–1.585	NS
SWS (min)	96.5 ± 6.2	148.2 ± 10.9	–5.128	**< 0.001**
SWS (%)	20.8 ± 0.7	25.4 ± 0.7	–5.393	**< 0.001**
REM latency (min)	94.4 ± 13.8	108.7 ± 13.4	–0.767	NS
REM (min)	107.6 ± 9.8	124.2 ± 9.9	–2.162	**0.05**
REM (%)	22.7 ± 1.2	21.4 ± 1.1	1.445	NS
MEN	**before**	**after**	**t (df=6)**	**p**
sleep latency (min)	311.0± 20.8	247.2± 34.1	1.814	NS
SE (%)	94.8± 1.2	98.3± 0.5	–1.156	NS
AST (min)	450.8 ± 27.8	518.0 ± 60.8	–1.313	NS
awakenings	13.0 ± 1.7	11.4 ± 2.0	0.755	NS
S1 (min)	28.3 ± 8.4	15.4 ± 3.1	1.380	NS
S1 (%)	5.4 ± 2.0	2.9 ± 1.2	1.430	NS
S2 (min)	224.8 ± 14.2	251.0 ± 34.7	–1.032	NS
S2 (%)	49.9 ± 1.6	48.0 ± 1.7	–3.736	**0.01**
S3 (min)	70.2 ± 5.5	95.8 ± 9.4	–2.304	NS
S3 (%)	15.8 ± 1.4	18.8 ± 0.8	2.269	NS
S4 (min)	29.6 ± 7.6	37.5 ± 6.3	–1.021	NS
S4 (%)	6.2 ± 1.5	7.1 ± 0.7	0.590	NS
SWS (min)	99.8 ± 7.8	133.3 ± 14.6	–2.222	NS
SWS (%)	20.5 ± 0.8	25.6 ± 1.0	2.695	NS/NP
REM latency (min)	99.7 ± 25.0	103.5 ± 21.8	–0.110	NS
REM (min)	106.4 ± 13.1	117.4 ± 13.5	0.853	NS
REM (%)	23.1 ± 1.7	22.9 ± 1.5	–0.146	NS
WOMEN	**before**	**after**	**t (df=5)**	**p**
sleep latency (min)	23.5± 13.9	201.7± 35.0	3.043	**0.03**
SE (%)	96.4± 1.7	96.0± 2.3	0.527	NS
AST (min)	473.4 ± 42.0	664.9 ± 39.1	–11.287	**<0.001**
awakenings	15.8 ± 3.6	15.5 ± 6.4	0.085	NS
S1 (min)	20.0 ± 8.4	17.7 ± 7.6	0.987	NS
S1 (%)	4.6 ± 2.3	3.0 ± 1.5	1.887	NS
S2 (min)	253.7 ± 25.2	349.5 ± 21.3	–9.569	**<0.001**
S2 (%)	52.9 ± 2.1	52.6 ± 1.5	0.403	NS
S3 (min)	61.8 ± 7.0	108.0 ± 11.3	–3.493	**0.02**
S3 (%)	13.2 ± 1.3	16.2 ± 1.4	–1.779	N
S4 (min)	31.0 ± 7.4	57.5 ± 16.3	–2.365	NS
S4 (%)	6.0 ± 1.1	8.4 ± 2.3	–1.461	NS
SWS (min)	92.8 ± 10.5	165.5 ± 14.3	–11.129	**<0.001**
SWS (%)	19.1 ± 0.8	24.7 ± 1.0	–6.780	**0.001**
REM latency (min)	88.2 ± 9.9	114.8 ± 16.1	–2.945	**0.03**
REM (min)	109.1 ± 16.1	132.2 ± 15.2	–3.054	**0.03**
REM (%)	22.3 ± 1.9	19.6 ± 1.6	2.835	**0.04**

Figure 5. Delta power in sleep recordings before and after administration of 10 mg olanzapine. Recording from a) a man and b) a woman. The cyclic structure of sleep is unaffected by olanzapine. The duration of sleep increased in the recording of the woman but not in the recording of the man after olanzapine. In the man, a slight increase in delta power is seen during the second sleep cycle while, in the woman, delta power appears to be increased in all four sleep cycles. One epoch is 30 s.



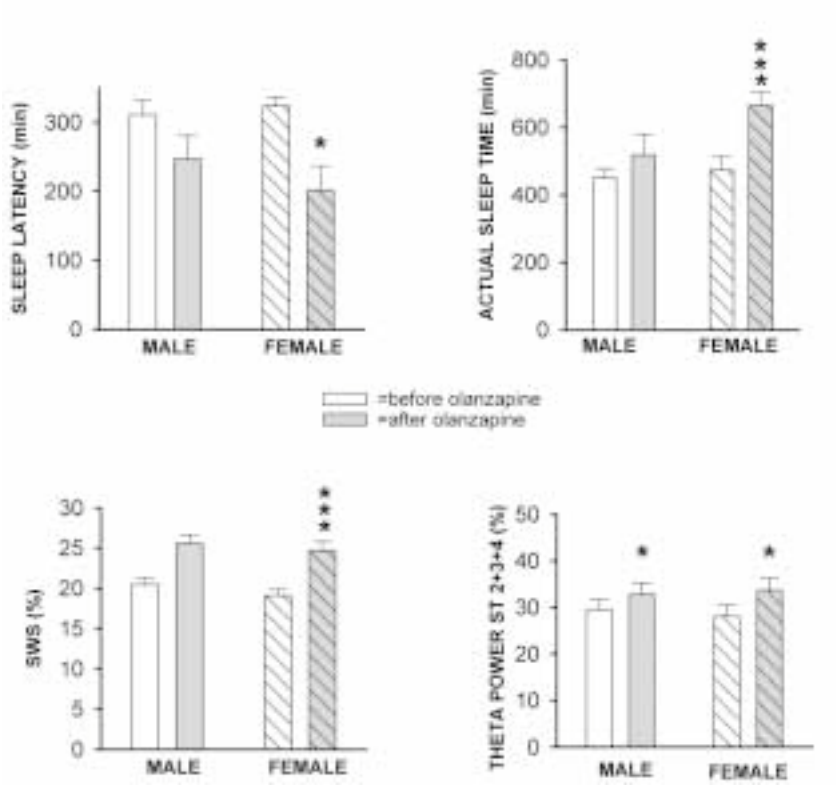
5. DISCUSSION

5.1. Methodological aspects

5.1.1. General

As a research method, PSG is a time-consuming procedure, which is fairly burdensome for a subject and for a researcher. It demands good collaboration between the two and is dependent on the subject‘s ability to follow the instructions. In addition, visual scoring of the sleep recording takes time and requires special expertise. These reasons at least partly explain the relatively small sample size, which is typically seen in PSG studies. This limitation is also seen in this work.

Figure 6. Results for polysomnography and spectral power analysis in seven men and six women before and after administration of 10 mg olanzapine. Comparisons were made using paired t-test (normally distributed values) or Wilcoxon signed rank test (non-normally distributed values). SWS = slow wave sleep, ST = stage.
* = $p < 0.05$, ** = $p < 0.01$, *** = $p \leq 0.001$



5.1.2. Sleep assessment

5.1.2.1. Diagnostic process

The important detail, which significantly affects the results of PSG studies is the comorbidity that is often seen among psychiatric patients. The ability to avoid or at least be aware of this confounding factor is based on a reliable diagnostic process which takes account of both axis I and axis II diagnoses.

One of the most common phenomena to take into account is the comorbidity of depression and the degree of it. Changes in sleep architecture have been documented most extensively in patients with major depression. In contrast, dysthymic patients tended to display sleep patterns similar to those of normal controls (Benca, 2000). In

a study by Cohen (1979), significant sleep disturbances were not seen in depressed patients who did not meet the criteria for major depression, and in individuals with depressed mood but not with mood disorder.

The inevitable consequence of the strict exclusion criteria, which aim to produce diagnostically "pure" study groups, is that the number of subjects often remains small, the findings must be regarded as indicative, and the conclusions must be drawn with care.

In AN in particular, PSG studies have yielded conflicting results (Levy et al., 1988). This is most probably due to the heterogeneous patient material, with variations in the degree of comorbidity between, and sometimes also within, the studies. We selected the patients with care in order ensure that they represented a uniform subgroup, so as to be able more accurately to describe the changes in the sleep. In the present study (I), the entire study group had the same subtype of AN and the degree of depression was only mild, and was probably secondary to the starvation state (Halmi, 2000).

All ASPs (II and III) were evaluated as highly aggressive with major psychological and social problems, but, they were nonetheless responsible for the violent acts they were being charged with. The opportunity to exclude ASPs with psychiatric disorders known to affect sleep architecture helped us to create a homogeneous group of habitually violent offenders with axis II diagnosis as the primary clinical diagnosis. As far as ASP is concerned, with prevalence rates of three percent for males in the general population (Cloninger and Svrakic, 2000), the study group represents an extreme subgroup even for a criminal population. For this reason, the results cannot be generalized to apply to the whole diagnosis group. Even among ASPs, the degree of depression was mild.

5.1.2.2. Placement of electrodes

In non-REM sleep the highest amplitude of theta power is in the posterior region (Werth et al., 1997) and this was the reason for choosing the O2-P4 derivation to maximize the detection of changes in theta power. As compared with the traditional Rechtschaffen-Kales (R-K) derivation (100%), the chosen derivation overestimates the detection of theta power (118%) and underestimates the detection of delta power (93 %). This suggests that using the R-K derivation the increase in theta power might have been slightly smaller and on contrary the increase in delta power even larger. The theta power was significantly higher in controls compared with anorectics and in anorectics after weight gain compared with anorectics before weight gain. The same kind of tendency was seen in delta power (I). Olanzapine significantly increased theta power in both sexes and, the same kind of tendency was seen for delta power (IV). It is possible to speculate that, if the R-K derivation had been used, the changes seen in delta power would have become statistically significant. Among ASPs, both delta and theta power were significantly higher compared with controls (II). Using the R-K derivation, the difference in delta power between ASPs and controls would have been even more significant.

However, both theta and delta power decline during the night and increase with the duration of wakefulness preceding sleep as markers of a homeostatic sleep process (Borbély et al., 1981), even if this homeostatic process has traditionally been defined through delta power. In fact, it seems that theta power acts as a sensitive indicator of sleep and sleep changes.

5.1.2.3. Registration environment

The results suggest that PSG monitoring in the patient's home is more sensitive than PSG in a sleep laboratory when it comes to documenting specific alterations in sleep (Hajak, 2000). The sleep recordings among healthy volunteers were made in a guest room of the psychiatric hospital (I–IV). The room was quiet and looked more like a bedroom than a sleep laboratory. On the other hand, spending the night in a mental hospital could have slightly worsened their quality of sleep. The situation was quite the opposite among ASPs (II–III). The structured daily activities and demand for silence during the night could have improved their sleep, opposite to that outside the hospital, suggesting that the present studies may underestimate the degree of sleep disturbances in their ordinary lives. However, the unstructured lifestyle of these males, with severe drug and alcohol dependence combined with abusive behaviour, would make a PSG study almost impossible to perform outside the hospital or the prison.

The first-night effect is a well-known phenomenon in sleep recordings and it is mainly characterized by lower SE, longer S2 and REM latencies, as well as a lower percentage amount of REM sleep. The effect has been shown to be more pronounced in healthy subjects than in psychiatric in-patients (Toussaint et al., 1995). It has become a common practice to exclude the first night of sleep from the analysis, and this was also done in our studies.

5.1.2.4. Age

It is well known that age affects the sleep architecture. The most easily recognized age-related change is the reduction in SWS observed by the age of approximately 20 (Bliwise, 1993). There is some disagreement about whether REM time or REM latency varies with ageing (Bliwise, 2000). In a study by Landolt et al. (1996), the effect of age on sleep was investigated in healthy older men (62.0 years) and young men (22.4 years) taking no medication. TST, SE and SWS were lower in older men, while S1 and wakefulness after sleep onset were higher. In this study, no changes in REM parameters, including REM latency, were seen between the groups. In older men, EEG power density in non-REM sleep was reduced at frequencies below 14.0 Hz, whereas related reductions in REM sleep were limited to the delta-theta (0.25–7.0 Hz) and low alpha (8.25–10.0 Hz) band.

AN has a bimodal peak of onset either between the ages of 14 and 15, or at the age of 18 (Halmi, 2000). One of the conflicting effects in sleep studies among anorectics is that these two different age groups are not always studied separately. In this work (I), the whole AN group consisted of the older subjects in order to create a homogeneous study group as well as it was possible.

The effect of age on sleep underlines the importance of matching when different study groups are compared. In our studies (I–III) no significant differences were seen between subjects and controls from this point of view. In Study IV, women were slightly older than men. However, both sexes slept equally well during the adaptation and placebo nights. As a result, the age difference, which was in fact fairly minimal, can hardly be seen as an explanation of the results.

5.1.2.5. Sex

In a study by Dijk et al. (1989) young adult age-matched men and women did not display any differences in the amount of SWS or REM sleep. SPA, however, detected significantly higher power densities during both non-REM and REM sleep over a wide frequency range (0.25–11.0 Hz) in the female subjects as compared with the male ones. The authors speculated that the changes might be caused by sex differences in skull characteristics, for example by the shape and bone thickness of the skull . In a study by Ehlers and Kupfer (1997), men and women in their twenties were also found to have similar percentages of SWS and mean EEG slow-wave activity. However, significant reductions in the percentage of SWS and mean slow-wave activity during the night occurred in men during their thirties but not in women. The findings suggest that the sleep in of men and women above age 20–40 may develop differently. So, although the effect of sex on sleep architecture is not dramatic, it should be taken into account when different study groups are compared. In our work (I–III), all the controls were sex-matched.

5.1.2.6. Weight

As sleep parameters as well as hormone secretion patterns are affected by weight (Benca and Casper, 2000; Veldhuis and Iranmanesh, 1996; Garnier et al., 1990) we selected the subjects with care in order to ensure that they represent a uniform group so as to be able more accurately to describe the changes in sleep and hormone levels. In study I, the starvation state was very serious at admission. The patients remained underweight even after the treatment period in hospital. In studies II and III the mean BMIs of the ASPs and controls did not significantly differ. However, the ASPs had stayed approximately 4 months in institutions with regular meals and limited physical exercise. One can assume that this kind of lifestyle is quite different compared with the one they are used to. This might have caused mild weight gain before the sleep examinations. Lacey et al. (1978) examined the immediate influence of intravenous amino acids and glucose on sleep as measured by PSG recordings in healthy women within a normal weight range. Both solutions increased SWS, while TST was not affected. The study indicates that body weight has a direct correlation to SWS. However, the changes reported by Lacey et al. were fairly minimal and hardly can be seen as an explanation of the significantly high amount of S4 sleep in ASPs. Willi et al. (1998) reported abnormally high SWS levels in adolescents with morbid obesity (mean BMI 50.9 kg/m^2), which tended to normalise with weight loss (mean BMI 5.4 kg/m^2). The authors attributed this change to significant amelioration of obstructive sleep apnea syndrome, the phenomenon not present in ASPs. In study IV the mean BMIs of women and men did not significantly differ.

5.1.2.7. Medication

Numerous prescription drugs for the treatment of both somatic and psychiatric disorders act within the central nervous system (CNS) and have the potential to affect sleep. Insomnia, sleepiness, sedation, and fatigue are common side-effects of many medicines. Sleep itself, as well as drug pharmacokinetics, is influenced by age and sex; it is therefore difficult to generalize on the basis of studies that are often conducted on young healthy male individuals. Moreover, healthy individuals may respond differently from the population for whom the treatment is intended. Many patients take a variety of drugs in combination, which may affect one another. Little research has been conducted on drug combinations (Schweitzer, 2000). To avoid these heterogeneous effects associated with medication, healthy volunteers and anorectics and ASPs were totally drug free during the entire registration period and two weeks prior to the first sleep registration. During the recording process, one of the volunteers was prescribed an sedative analgesic (tramadol hydrochloride) for a transient headache by his doctor and was excluded from the study (IV). The anorectics for whom medication was started in order to facilitate the healing process were also excluded from the sleep examinations made after the weight gain (I).

5.1.2.8. Alcohol and illicit drugs

As described earlier (1.7. Alcohol and sleep) alcohol affects sleep significantly both in dependence syndrome and in the withdrawal state. ASP is frequently combined with substance abuse (Robins, 1998). In Study III, 16 of 19 ASP offenders were also alcoholics, representing Cloninger early-onset type 2 alcoholism. However, the ASPs had spent over four months in prisons or hospital with no alcohol intake. Therefore it seems improbable that their sleep would have been affected by alcohol withdrawal syndrome. In the light of previous PSG studies of type 1 alcoholism, it is also improbable that the results, with large amounts of SWS and S4, could be explained by comorbidity with alcoholism.

Relatively few studies have investigated sleep patterns during illegal drug use or after withdrawal from drug dependence. Amphetamine and other stimulants have been reported to prolong sleep latency and reduce TST. They also affect REM parameters, resulting in increased REM latency and reduced REM % (Gillin and Drummond, 2000). The sleep abnormalities related to stimulant withdrawal include reduced SE, increased nocturnal wake time, increased S1 and REM sleep, and shorter REM latency. These sleep abnormalities remained for at least the first two weeks of abstinence (Watson et al., 1972). The short-term administration of opiates to normal controls or abstinent addicts reduced SE, TSL, SWS and REM sleep (Kay et al., 1981). With chronic administration, the REM-suppressing effects of morphine were lost within a week (Staedt, 1996). In a study by Feinberg et al. (1976), the effects of delta-9-tetrahydrocannabinol (TCH) in PSGs were studied in four experienced male marijuana users. The S4 sleep tended to increase with drug administration. An abrupt withdrawal led to an increase in REM sleep, and a sharp fall in S4 to baseline levels was seen. Many of the ASPs (II–III) were also dependent on drugs. The drugs that were primary used were cannabis and amphetamine. In fact, in this study group, there were no individuals with opiate dependence. The occasional use of illicit drugs during imprisonment is, unfortunately, not completely excluded, but the urine

screenings for illicit drugs were made just before the sleep examinations and they were negative in all cases. The approximate duration of the detectability of cannabis is approximately 10 days in the case of recreational users and three to four weeks in the case of heavy users (Gillin and Drummond, 2000). So, it is unlikely that the results, especially the increase in S4, could be explained by the abuse of cannabis.

5.1.2.9. Caffeine

Caffeine and other methylxanthines are stimulants that are found not only in coffee but also in tea, cola and cocoa. A normal cup of brewed coffee contains about 100 to 150 mg of caffeine. Individuals differ in their response to caffeine, some people being over-stimulated by as little as 250 mg (Gillin and Drummond, 2000). Although the half-life of caffeine is about three to seven hours, the effects may last for as long as eight to 14 hours (James, 1998). Caffeine clearance in chronic hepatitis patients has been reported to be significantly lower than in normal subjects (Wittayalertpanya et al., 1996). So, caffeine may have significant effects on sleep at night, even if it is consumed in the afternoon or early evening. From the perspective of sleep-wake regulation, caffeine appears to promote wakefulness by blocking adenosine receptors in the brain (Gillin and Drummond, 2000). Many people, however, develop tolerance, and apparently sleep well, according to subjective reports (Gillin and Drummond, 2000). The Finns consume large quantities of coffee, and especially among psychiatric inpatients coffee drinking is very important as a social habit. To promote compliance, the participants were allowed to consume their normal amount of caffeine.

5.1.2.10. Nicotine

Nicotine dependence is about two to three times higher in patients with mental disorders than in normal population. The plasma half-life of nicotine is about 2 hours and for the average smoker, who smokes throughout the day, plasma concentration of nicotine increases over the course of the day and falls throughout the night, although it remains detectable in the morning (Gillin and Drummond, 2000). Both PSG and questionnaire studies have reported increased sleep latency as well as difficulty to stay asleep at night in active smokers compared with non-smokers (Davila et al., 1994). Acute nicotine withdrawal has been reported to increase arousals and number of awakenings during night (Wetter et al., 1995). Nicotine replacement therapy has been shown to decrease this sleep fragmentation and increase the amount of SWS as a recovery effect after sleep deprivation associated with the withdrawal state (Wetter et al., 1995). To promote compliance, the participants were allowed to smoke their normal amount of cigarettes. Opposite to other subjects and controls, most of the ASPs were heavy smokers with approximately 20 cigarettes a day. However, in the light of previous PSG studies of tobacco smoking, it is improbable that the results, with large amounts of SWS and S4, could be explained by nicotine dependence.

5.1.2.11. Brain traumas

Brain contusions produce gliotic scars or focal atrophy as long-term sequelae. These focal abnormalities most probably affect the patient's sleep architecture, although no PSG follow-up studies in this field are available. A brain MRI (1.5T) was performed on both subjects and controls (II-IV) and no post-traumatic signs in the brain sub-

stance were reported. Among ASPs, the waking-EEGs were also within normal limits, except in four cases with mild slowing of background activity without focal or paroxysmal changes.

Minor head injuries (concussions) are, however, frequent events among ASPs. Kaufman et al. (2001) demonstrated a chronic sleep disturbance several years after a minor head injury in a non-selected population. They found lower SE and more awakenings lasting more than three minutes, but no changes in S3 or S4 as compared with healthy controls. It therefore seems improbable that the results, which show an increase in SWS and S4 among ASPs, were a consequence of traumatic brain injury.

5.2. Sleep, GH-IGF-1 and leptin in anorexia nervosa

Our findings relating to the reduction in sleep duration and SWS, as well as the increase in S1 sleep in AN are in good agreement with previously published studies (Walsh et al., 1985; Levy et al., 1988). We observed no changes in REM parameters, including REM latency. This most probably reflects the mild degree of depression in the patients in the present study (Katz et al., 1984).

In most sleep studies of AN, weight gain has increased SWS (Crisp et al., 1971; Lacey et al., 1975; Lauer and Krieg, 1992). This was also the finding in the present study. Lacey et al. (1975) reported that, during refeeding and weight gain, SWS initially increased, and then tended to decrease during the final stage of restoration of weight to matched population mean levels The results of the present study revealed a rapid normalization in SWS after only a limited weight gain, while the duration of sleep remained shorter than in controls. It may be argued that SWS is critically important, and the propensity for SWS is restored primarily after a period of shortage, as evidenced, for example, by sleep deprivation and recovery sleep experiments (Carskadon and Dement, 2000).

Higher IGF-1 levels were associated with an increase in SWS in anorectic patients. A similar finding in elderly men has been reported previously (Printz et al., 1995). The finding suggests that sleep quality in anorectics might be related to the status of their GH-IGF-system. Leptin levels correlate with the amount of fat stores and changes in energy balance as a result of fasting (Ahima et al., 2000). In animals, the depletion of energy stores tends to favour wakefulness and activity to seek food (Danguir and Nicolaidis, 1979). In the present study, higher leptin levels were associated with longer and deeper sleep among both healthy controls and anorectics. In addition, low levels of leptin correlated with “light” sleep in AN. We are not aware of any previous reports on the relationship between leptin levels and human sleep. In the present study, the single sample of GH collected in the morning did not reveal significant differences between the AN and controls. This result resembles the findings of Nussbaum et al. (1990) and Golden et al. (1994). Golden et al. (1994) postulated that patients with AN may exhibit low GH levels at the onset of the disease. If the energy deprivation is maintained in a chronic state of disorder, the patients may develop GH resistance, leading to a rise in GH. The mean duration of the disorder in our patients was only 2.2 years, suggesting that the condition was not yet chronic. This may be the reason for our findings of low GH levels.

IGF-1 appears to be a marker of malnutrition, and a sensitive index of nutritional repletion in patients with eating disorders (Caregaro et al., 2001). Hill et al. (1993) reported a stepwise increase in IGF-1 values related to weight gain in anorectic patients. Our finding of an increase in IGF-1 during weight gain is in good agreement with their results. The increase in serum leptin levels as a consequence of weight gain resembles the findings of both Grinspoon et al. (1996) and Casanueva et al. (1996). The hormones of the GH-axis, as well as leptin, have been found to increase SWS (Steiger et al., 1992; Sinton et al., 1999), with insignificant effects on REM sleep. The finding in AN patients that SWS was reduced while REM sleep remained unaffected strengthens the view that the sleep disturbances in AN are linked to changes in hormone secretion.

In conclusion, we found reduced levels of GH-axis hormone IGF-1 and leptin, as well as reduced SWS and theta power, in patients with AN. After a limited weight gain, the levels of IGF-1 and leptin increased, as did SWS and theta power. These results are in agreement with previous studies of AN, and strengthen the view that sleep problems in AN are closely associated with the physiological starvation state.

5.3. Sleep in habitually violent offenders with antisocial personality disorder

The most striking finding in ASP males was the increase in SWS, and, in particular, the amount of the deepest sleep stage, S4. Good agreement with the increase in SWS from scoring data and the increase in delta (and theta) power from the spectral analysis further confirm the validity of the sleep analysis.

Attention deficit hyperactivity disorder (ADHD) is a risk factor for ASP (Gittelman et al., 1985; Mannuzza et al., 1993). Children with ADHD have been reported to have a deficit in alertness (Lecendreux et al., 2000). They were described to be more sleepy during the day, to have longer reaction times and to fall asleep faster than controls. Many studies of attention deficit disorder (ADD) children have found no changes in SWS compared with controls (Palm et al., 1992; Corkum et al., 1998; Picchietti et al., 1999). Platon et al. (1990), however, reported a PSG study of 13 non-medicated prepubertal children with attention deficit disorder (ADD). In this study ADD-children experienced a large number of nocturnal awakenings and a higher SWS percentage compared with normal age-matched controls. In addition, the two subtypes of the disorder - ADHD and ADD without hyperactivity- displayed distinct polysomnographic correlates. Children with ADHD had a greater sleep fragmentation and a lesser degree of SE. In a study by Picchietti et al. (1999) the prevalence of periodic limb movements in sleep (PLMS) was higher in the children with ADHD than in the control subjects. We are not aware of any PSG studies in adult ADHD. Many of our ASP males had features of ADHD connected with conduct disorder in their history, and it is possible to speculate that the abnormalities seen in polysomnography can be partly explained by residual effects of childhood ADHD. This is, however, virtually impossible to verify retrospectively.

One of the consistent alterations in normal ageing is a reduction in SWS, while REM sleep is less affected (Bliwise, 2000). The sleep patterns of children are characterized by large amounts of SWS (Bes et al., 1991). A quantitative change in SWS occurs

during puberty and a reduction in SWS of almost 40% during the second decade of life has been reported (Carskadon and Dement, 2000). As ageing proceeds, a gradual decline in SWS is observed (Bliwise, 2000). In the present study, ASP males at the age of 31 years had 17.2% S4, compared with the 6.3% in controls. The amount of S4 in the 31- year-old male controls of the present study is in good agreement with previously published studies: 5.9 % in 25-year-old men (Steiger et al., 1992) and 7.0% in 35- year- old women and men (De la Fuente et al., 2001). While the amounts of SWS and S4 were high in the ASP, both parameters correlated negatively to age, as in the normal population. It is possible, that the decline in SWS that normally occurs in the course of ageing, is delayed in ASP. ASP tends to become less evident or to remit with age (APA, 2000). Whether the change in behaviour is correlated to changes in SWS remains to be clarified with further studies.

5.4. Sleep research perspective of human impulsive aggression

To our knowledge, this is the first study to compare sleep in ASP with and without BPD comorbidity. The most striking finding was the disruption in the continuity of sleep in persons with both personality disorders. This finding is similar to the results reported in PSG studies of borderline persons with no ASP comorbidity (Battaglia et al., 1993; De La Fuente et al., 2000). In ASP with and without BPD comorbidity, the amount of S4 sleep was equally high and significantly higher than in controls. So, in spite of many overlapping clinical features, the sleep architecture in these two personality disorders appears to differ and, in cases with comorbidity, both disorders have their own characteristics that influence sleep. The result is in agreement with the finding that ASP differs from that with BPD comorbidity both in research settings and clinical outcome (Coid, 1993; Virkkunen et al., 1996; Herpertz et al., 2001).

It has been obvious for some time that aggressive behaviour in childhood is the most stable of all early detectable personality characteristics (Loeber, 1982). The total number of CD symptoms was reported to be the most important predictor of future ASP (Robins, 1991). In the study by Stattin and Magnusson (1989), high ratings for aggressiveness were characteristic of boys who subsequently committed violent crimes and damage to public property. In our study of habitually violent offenders, half the subjects were estimated to have severe CD and half were regarded as having either mild or moderate CD in their history. The sleep parameters related to ASP, SWS and especially S4, as well as theta and delta power in these sleep stages, associated strongly with the severity of previous CD. Those subjects with a large number of CD symptoms in their childhood had a very large amount of delta sleep measured in adulthood. This raises the interesting question of whether this exceptional deep-sleep pattern had already developed in childhood or adolescence in these males? In a sleep study by Coble et al. (1984), a larger number of delta waves were found in boys with a primary diagnosis of CD compared with age-matched healthy controls, suggesting that this deep-sleep pattern may indeed already develop in childhood or during adolescence. The subjects in the Coble study were 17 pre-adolescent boys and, in fact 13 of them represented the undersocialized aggressive subtype according to DSM III, which was regarded as the most serious form of CD. To qualify as a case of the aggressive form, the conduct had to include robbery or violence against persons or property, and for a case to qualify as undersocialized, there could be no more than

one of five indicators of being "socialized": enduring friendships, altruistic behaviour, feeling guilt or remorse, refraining from blaming others, and showing concern for others (APA, 1980). It is possible to speculate that these boys in the study by Coble et al. would be the most likely to become antisocial in adulthood. Raine et al. (1990) reported a retrospective waking EEG study of 101 men. It showed that adult criminals, at the age of 24, had significantly more slow-frequency (delta and theta) electroencephalographic activity than non-criminals at the age of 15 years. The authors speculated that, in addition to social and psychological variables, measures of both autonomic nervous system and central nervous system underarousal may facilitate the early prediction of subsequent antisocial behaviour and even elucidate the etiological basis of criminality.

The notion that explosive violence may be linked to a discrete diagnosable condition such as IED is still controversial. S4 sleep was significantly higher in men with IED compared with those without this diagnosis. In fact, non-IED subjects did not differ in this respect from healthy controls. The relationship between S4 and highly impulsive extreme aggression underlines the dimensional aspect of human aggressive behaviour. The result is also in agreement with previous studies suggesting that there might be different subpopulations within ASP with a varying degree of impulsiveness (Linnoila et al., 1983; Coccaro et al., 1989; Virkkunen et al., 1996; Barratt et al., 1997; Coccaro et al., 1998; Coccaro 2000). Future research is needed to clarify whether the relationship between S4 and IED is limited to ASP or can also be found in other populations, such as mentally-retarded patients with serious impulsive aggression.

5.5. Testosterone and sleep in persons with impulsive aggression

In the present study, there were no differences in serum testosterone levels between antisocials with (20.4 nmol/L, SEM 1.74, age-adjusted 19.6 nmol/L, SEM 0.45) and without BPD comorbidity (20.6 nmol/L, SEM 2.66, age-adjusted 21.9 nmol/L, SEM 0.88). On the other hand, there was a significant difference between antisocials with severe CD (24.1 nmol/L, SEM 1.83, age-adjusted 23.5, SEM 0.52) and those with only mild or moderate CD (16.9 nmol/L, SEM 1.27, age-adjusted 17.4 nmol/L, SEM 0.52). This finding is in accordance with the study by Brooks & Reddon (1996), which reported higher single morning serum testosterone levels in 15-17-year-old violent offenders with CD compared with boys committing non-violent or sexual offences. The antisocials with IED (21.8 nmol/L, SEM 1.65, age-adjusted 21.3 nmol/L, SEM 0.51) displayed a tendency towards higher serum testosterone levels than those without the diagnosis (16.4 nmol/L, SEM 2.10, age-adjusted 17.4 nmol/L, SEM 1.05). If IED is regarded as a categorical expression of recurrent problematic impulsive and aggressive behaviour as expressed by Coccaro (2000), it is possible to speculate that in this subgroup of antisocials, the criminal recidivism would be emphasized. In the study by Räsänen et al. (1999), recidivists with personality disorder had higher testosterone levels than non-recidivists with personality disorder. One of the limitations of the present work is the absence of serum testosterone measurements in control subjects. The comparisons were limited to the different subgroups of ASP. However, in the study by Räsänen et al (1999), the serum testosterone levels of the healthy controls with approximately equal age compared with

the controls in this study (36.4 years, SD 8.0) were mean ± SD 16.8 ± 4.7 nmol/L, age-adjusted 17.5 nmol/L. In both patient groups with higher serum testosterone levels (preceding type severe CD and IED), the percentage amount of S4 sleep and the theta power in stages 4 and 3+4 were also significantly higher. The role of diurnal testosterone secretion in regulating normal human sleep is still unclear. Serum testosterone levels have been described as being lower when young healthy adult men were awake than during sleep (11 pm-7 am). The levels began to rise when the subjects fell asleep, and reached their peak value at about the time of the first REM cycle, remaining at the same levels until awakening (Luboshitzky et al., 1999). In the study by Leibenluft et al. (1997), leuprolide acetate was used to produce pharmacologically- induced short-term hypogonadism in men of 18–48 years. Interestingly, this procedure only caused significant reductions in the amount of S4 sleep compared with measures taken during testosterone replacement. This connection between S4 sleep and testosterone, despite being associated with the testosterone-replaced state, offers an opportunity to speculate about whether, in violent offenders with ASP, the increased amount of S4 sleep is perhaps at least partly mediated via elevated testosterone levels.

5.6. The effect of a single dose of olanzapine on sleep in healthy women and men

The structure and continuity of sleep were unaffected by olanzapine in both sexes. Olanzapine appears to preserve the normal structure of sleep, which is of significant benefit in the treatment of schizophrenia and increase the amount of SWS. The important finding was that the same dose of olanzapine in women induced a clear increase in sleep length, while in males the increase was either absent or small, indicating that the effective dose of olanzapine on sleep may be lower in women. The body weights or body mass indexes of men and women did not differ, suggesting that a simple dose relationship could not explain differences in sleep parameters. The half-life of olanzapine is longer (36.7 vs. 32.3 h) and the clearance is lower (18.9 vs.27.3 L/h) in women than in men (Research File, Eli Lilly and Company) and this is attributed to the differences in CYP1A2 activity between the sexes. In healthy subjects, a single dose of olanzapine induces a peak plasma concentration (Tmax) in five hours (Kassahun et al., 1997). A difference in plasma concentrations of olanzapine between male and female patients with schizophrenia after a similar dose of olanzapine has been reported (Kelly et al., 1999), but this difference only became evident after five weeks of treatment. It is therefore possible, but not probable after a single drug dose, that the sex differences seen in this study could be explained by the longer half-life and lower clearance in women.

Olanzapine most probably affects sleep through many neurotransmitter systems. The decrease in sleep onset is probably mediated via the blockade of histamine –H1 receptors (Reus, 1997). In women, the REM-parameters changed significantly, and as the relative amounts of stage 1 and 2 sleep remained unaffected, these changes probably reflected the increase in the relative duration of SWS. This effect may also result from the antagonistic effects of olanzapine on muscarinic cholinergic receptors. The association between SWS and 5-HT2 receptors is well established (Idzikovski et al., 1986; Dugovic and Wauquier, 1987). Ritanserin, a specific 5-

HT2A/ 2C receptor antagonist doubled the absolute amount of SWS in healthy volunteers (Idzikowski et al., 1986; van Laar et al., 2001). In a study by Sharpley et al. (2000), olanzapine was reported to produce substantial and highly significant dose-related increases in SWS in humans, probably via the blockade of brain 5-HT2C receptors.

The 5-HT2C receptor gene has been localised to the X chromosome (Xq24) and contains a C-G polymorphism at codon 23 (nucleotide 68) such that serine replaces cysteine in the receptor in about 10–25 % of the different populations (Lappalainen et al., 1995; Lerer et al., 2001). Because of the localisation in the X chromosome, men can be only either Ser or Cys, but women can have Ser-Ser, Ser-Cys or Cys-Cys allelic variants. Sharpley et al. (2001) described polysomnographic findings in 24 drug-free men, twelve of whom were Ser variants and 12 Cys variants. The acute administration of 5 mg of olanzapine had significant effects on SWS, sleep latency, SE, wakefulness after sleep onset, stage 1 sleep and REM-sleep latency, but no significant genotype effect or olanzapine by genotype interaction. Among women, because of different homotsygotic allelic variants, olanzapine may, however, cause greater changes in sleep parameters. Further research into these functional 5-HT2C gene variants is, however, needed.

6. CONCLUSIONS

The main results and conclusions are:

1. Reduced levels of the GH-axis hormone IGF-1 and leptin, as well as reduced SWS and relative theta power, were found in patients with anorexia nervosa. After limited weight gain, the levels of IGF-1 and leptin increased, as did SWS and theta power. These results are in agreement with those in previous studies of anorexia nervosa, and strengthen the view that sleep problems in anorexia nervosa are closely associated with the physiological starvation state.

2. Increased deep sleep, especially S4, and increased relative delta and theta power, were associated with habitually violent male offenders with antisocial personality disorder. Whether this sleep architecture reflects a specific brain pathology, or a delay in the normal development of sleep patterns in the course of ageing, needs to be clarified with further experiments.

3. The offenders with preceding type severe conduct disorder had higher amount of S4 sleep and higher relative theta and delta powers in this sleep stage compared with males with only mild or moderate conduct disorder. The same kind of sleep architecture was associated with intermittent explosive disorder.

4. Among habitually violent offenders, in the subgroups with higher serum testosterone levels – preceding type severe conduct disorder and intermittent explosive disorder – the amount of S4 sleep as well as relative theta and delta powers in this sleep stage were increased.

5. Olanzapine appears to preserve the normal structure of sleep, which is of additional significant benefit in the treatment of schizophrenia and increase the amount of SWS. The same dose of olanzapine in women induced a clear increase in sleep length, while in men the increase was either absent or small, indicating that the effective dose of olanzapine on sleep may be lower in women.

7. FUTURE CONSIDERATIONS

Although ASP is diagnostically always preceded by CD before the age of 15 (APA, 2000), not much is known about the physiological mechanisms that are involved in this process. Autonomic underarousal and a low resting heart rate are reported to be the best-replicated biological correlates of antisocial and aggressive behaviour in child and adolescent populations. It has also been suggested that damage to the prefrontal cortex (PFC) can lead directly to antisocial, aggressive, and criminal behaviour among children (Raine, 2002). From the perspective of sleep research, the important question is whether the deep-sleep phenomenon reported in adult ASPs can already be seen in children or adolescents with severe CD. The possible relationship between CD and SWS needs to be clarified with future polysomnographic studies. Prospective follow-up studies are also needed.

Neither CD nor delinquency is rare among girls. As adults, antisocial girls have been shown to manifest increased mortality rates, substantial rates of psychiatric morbidity, dysfunctional and often violent relationships, and high rates of multiple service utilization. The rate of violent crimes among girls and women appears to be increasing (Pajer, 1998; Lewis et al., 1991). One in every five female prisoners has been reported to have ASP (Fazel and Danesh, 2002). However, it is still unclear whether the impulsive, aggressive behaviour among women is affected by the same biological mechanisms as among men. From the perspective of sleep research, another important question is whether this exceptional deep-sleep phenomenon reported in men with ASP can also be seen among antisocial women.

Many studies confirm the association between violence and schizophrenia, and an over-representation of people with schizophrenia has been reported in offender populations (Walsh et al., 2002). Schizophrenia patients with ASP represent a special high-risk subgroup that is vulnerable to severe substance abuse, psychiatric impairment, aggression and legal problems (Mueser et al., 1997). There are no sleep studies of violent patients with both schizophrenia and ASP, and the interesting question is whether the deep-sleep phenomenon can be seen among them, even though schizophrenia is typically associated with reduced SWS. Clozapine, an atypical antipsychotic with significant anti-aggressive effects (Fava 1997; Chengappa et al., 1999; Chengappa et al., 2002), is widely used in institutions where habitually violent schizophrenia patients are treated. Interestingly, in a study by Hinze-Selch et al. (1997), clozapine significantly reduced the amounts of S4 and SWS in patients with schizophrenia. However, also olanzapine has been reported to reduce severe aggression (Söderström et al., 2002), and opposite to clozapine, it increases SWS.

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