Arousal indices, cognitive function and effects of modafinil in Sleep Apnea patients: a pilot double-blind, placebo-controlled study for the validity of a modified Pupillary Sleepiness Test

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ABSTRACT

The present project attempts to clarify the effects of the cognitive and vigilance enhancer drug modafinil on indices that measure daytime sleepiness and obstructive sleep apnea (OSA) and the validity of a modified pupillary test for the objective measurement of daytime somnolence.

The research was conducted in sleep-apnea patients of all severities that had not received any treatment before and during this study. The results first of all suggest that the new pupillary sleepiness test (PST) is a quite sensitive tool for the assessment of daytime sleepiness. Pupil diameter, which is measured by this test, seems to be larger during alertness (morning hours) and much decreased during sleepiness and fatigue (in the afternoon). Moreover, polysomnographic (PSG) indices of the severity of sleep apnea – a sleep disorder that includes daytime sleepiness - are significantly correlated with pupil size, under the effect of somnolence. Thus, the more severe sleep apneics appear to have the smaller pupils. However, subjective tests that measure sleepiness (Epworth Sleepiness Scale, ESS) show a relationship with pupil diameter of sleepy patients but only under the effect of body indices, which means that fat people have the tendency to feel sleepier than people who are not fat.

Treatment of apneics with the wake-promoting drug modafinil increases significantly pupil diameter. The effect of modafinil on pupil size was greater in the more severe sleep apneics and in patients with the higher subjective sleepiness (ESS). After partialling out the effect of body fat indices, modafinil's effect correlated even more significantly with subjective sleepiness. So, PST seems to be affected by the vigilance-enhancing drug modafinil. Modafinil has been also found to reduce the amplitude of light reflex, while causing no effect on the 75% recovery time (return of pupil on the 75% of its initial diameter) or cardiovascular parameters. These findings demonstrate that the drug increases central parasympathetic activity but does not affect the sympathetic tone.

Finally, modafinil seems to improve patients' performance on neuropsychological tests (RTI, RVIP, SoC), which depend on mechanisms that induce alertness.

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I. GENERAL INTRODUCTION

Ia. Sleepiness/Somnolence and Wakefulness/Alertness

Sleep-wake cycle

Sleep is a repeated, physiologic and easily diverted state, which is related to various physiologic changes, such as breathing, heart function, body pulses and temperature, muscle tone and hormone release. Many researchers refer to the significance of sleep, as a homeostatic mechanism and part of the sleep-wake cycle (Caplan et al., 2000).

The sleep-wake cycle of mammals is divided into three states according to distinct behavioural and neurophysiologic characteristics: wakefulness, non-REM (Rapid Eye Movement) sleep and REM sleep. Based on the sleep-wake cycle, wakefulness is characterized as a behaviourally interactive state, with full consciousness, fast activity on electroencephalography (EEG), conscious eye movements and high muscle tone activity. Non-REM sleep is a behaviourally quiet state with reduced responsiveness to environmental stimuli and low EEG and motor activity. REM sleep is the phase of rapid, unconscious EEG and motor activity with complete absence of responsiveness to external stimuli. Normal sleep is thought to pass from wakefulness to non-REM and, then, REM sleep (Jones, 1998).

Sleep and wakefulness, like many behaviours and physiological activities have a circadian periodicity of about 24 hours. During that time most adults sleep one or two times (about 8 hours of sleep every day) (Caplan et al., 2000; Kandel et al., 2000). Circadian rhythms are endogenous, but under normal circumstances are modulated by external cues (such as sunlight) (Kandel et al., 2000). There is a normal variety in sleep-wake cycle depending on age (infants and children sleep longer, while aged people sleep less than usual) or sex (women often change their sleep-wake cycle during the month) (Caplan et al., 2000).

Since circadian rhythms are endogenous they have an internal clock. One major internal clock in mammals is the suprachiasmatic nucleus of the anterior hypothalamus,

although this tract is not responsible for sleep itself. It is believed that there is not a single sleep center that controls sleep or wakefulness, but many brain structures, which participate in the regulation of sleep and alertness. These are: brainstem reticular activating system, locus coeruleus, dorsal raphe and other brainstem nuclei, basal forebrain, thalamus, hypothalamic loci and cortex (McCarley, 1999). Their interaction probably produces sleep, alertness/wakefulness or excessive daytime sleepiness (EDS) and several other sleep-wake disorders.

Many neurotransmitters and neuropeptides are known to be implicated in the expression of sleep and alertness. Specifically, the monoamines serotonin (5-HT) and norepinephrine (NE), dopamine (DA), histamine (HA), hypocretin (orexin), acetylcholine, gamma-aminobutyric acid (GABA), glutamate, substance P, interleukin-1, prostaglandis and adenosine participate in sleep-wake regulation. It is suggested that alteration in acetylcholine, NE, 5-HT and HA are more involved in regulating the cortical characteristics of wakefulness, whereas dopaminergic activity is thought to mediate motor-related aspects of behaviour (Chemelli et al., 1999).

'Sleepiness/somnolence' and 'wakefulness/alertness' are two behavioural, physiologic states (Poceta et al., 1992). The word sleepiness is used by different people to mean different things: from a set of subjective feelings that accompany the drowsy state to physiological changes (such as in the pupil) that occur during the sleep onset process (Johns, 1998). Patients may name it as 'tiredness', or 'fatigue', thus leading to semantic confusion (Guilleminault & Brooks, 2001). There are as many different kinds of sleepiness as there are different situations in which to measure it (Johns, 1998). Sleepiness is a physiologic drive-such as hunger or thirst-which promotes the onset of sleep and is often reversed by the attainment of adequate sleep (Guilleminault & Brooks, 2001). In most individuals sleepiness is not severe and is usually alleviated after extended nocturnal sleep. But for other people the drive to reduce sleepiness may be so overwhelming that it interferes with other activities and may even cause health and safety ramifications (Broughton et al, 1981; Horne & Reyner, 1995).

According to the National Commission of Sleep Disorders (1993) 10 million people suffer from impaired alertness, while excessive daytime sleepiness affects up to 12% of the general population (Klink & Quan, 1987). EDS, rather than insomnia, is the

most common complaint of patients seen in sleep clinics (Roth et al., 1994; Weitzman & Fry, 1989; Report of American Academy of sleep Medicine Task Force, 1999). It is known as the main characteristic of many neurologic disorders (Broughton et al., 1997), including Alzheimer's disease and other dementias, Parkinson's disease, peripheral neuropathy, neuromuscular disorders, epilepsy and chronic pain syndromes (Guilleminault & Brooks, 2001). Both excessive daytime sleepiness and fatigue are highly prevalent in primary care and in specialty medicine and have a negative impact in quality of life (Pigeon et al., 2003). However, EDS is usually a symptom of primary sleep disorders (Johns, 1998), such as apnea (Young et al., 1993) and periodic limb movement disorder, whereas fatigue is thought to be consistent with insomnia (Guilleminault & Brooks, 2001) and disorders such as depression (Smith, 1992), cancer (Glaus, 1998) and epilepsy (Manni & Tartara, 2000).

Measuring Sleepiness

Various tools have been developed to assess sleepiness objectively and subjectively. These tools explore different aspects of sleepiness. Thus, several instruments can be used to evaluate a single patient.

The main tools that measure sleepiness objectively are:

a) The Multiple Sleep Latency Test (MSLT)

The MSLT - the main test for identifying narcolepsy - is an objective measure of physiologic sleep tendency in a setting which controls both behavioural and environmental factors (Mitler et al., 1982). It was first created to measure the sleep latency but was soon used in order to distinguish normal from abnormal daytime sleepiness (Carskadon et al., 1986). The MSLT is usually performed after nocturnal polysomnographic recording and measures how quickly the subject falls asleep when asked to do so. The test includes a series of 4-5 scheduled naps, during which the time to sleep onset (sleep latency) as well as the stages of sleep during the naps are recorded (Van dev Hoed et al., 1981; Carscadon, 1994). The subject is asked to lie down in a quiet, darkened bedroom, while attached to electrodes (Richardson et al., 1978). A mean Sleep Latency (SL) of 10-20 minutes is normal, while 5-10 minutes of sleep latency represents

a ‘diagnostic grey area’ and SL<5 minutes ‘pathological sleepiness’ (Carskadon et al., 1986).

It is thought to be valid, reliable and objective, the ‘gold standard’ for measuring daytime sleepiness (Carskadon et al., 1986) in a controlled, laboratory setting (American Sleep Disorders Association, 1992). Its value varies, depending on the time of day, previous sleep deprivation or treatment with sedative or stimulant drugs (Thorpy, 1992). But, no matter how accurately and objectively MSLT measures sleepiness, it is restricted only in one test situation and for that reason cannot be relied upon as an accurate predictor of sleepiness in different situations (Johns, 1994, 1998) .

b) The Maintenance of Wakefulness Test (MWT) (Carskadon et al., 1986; Mitler et al., 1982; U. S. Modafinil in Narcolepsy Multicenter Study Group, 1998)

The MWT was initially invented as a modification for the MSLT (Poceta et al., 1992). It is an objective measure of alertness, which measures the ability to maintain wakefulness. The subject is placed in a comfortable position (sitting in a bed, resting against pillows), in a quiet dimly lit room, attached to electrodes, while asked to stay awake for 20 (or 40) minutes (Carskadon et al., 1986; Mitler et al., 1982). The measure of sleepiness in this test refers to the mean sleep latency determined from 4 (or more) naps (Roehrs & Roth, 1992). It is usually used to confirm the absence of pathological sleepiness (Pigeon et al., 2003).

The MWT is very valuable when there are clinical questions, such as how capable is the patient of remaining awake in a sedentary situation (driving, watching TV etc) (U.S. Modafinil in Narcolepsy Multicenter Study Group, 1998). However, measurement of the ability to stay awake may be also affected by other factors, such as the time of day, environmental conditions and motivational factors, which are not taken unto account by this test (Roehrs & Roth, 1992).

Both MSLT and MWT require that the patient stays in the laboratory for an entire day and are sensitive to patient’s attitudes (Lavie et al., 1995). The main differences between the two tests include the subject’s posture (lying or sitting in bed), the degree of support for the head (resting against pillows or not), having eyes open or closed, staying in a dimly lit or dark room, giving the instruction to stay awake or try to fall asleep (Johns, 2000). Correlations have shown that only 20-25% of variance is shared by these two tests

(Sangal et al., 1992; 1997). MSLT and MWT are better suited for more rapidly repeated measurements of one situational sleep propensity (Johns, 1991).

c) nocturnal Polysomnography (nPSG),

Polysomnography also measures objective aspects of sleep. This technique evaluates electroencephalographic, electro-oculographic, electromyographic, cardiovascular, respiratory, gastrointestinal and other measures over an entire night's sleep and during various sleep stages. Polysomnography is also used to detect specific sleep abnormalities, such as sleep apnea and periodic limb movements, either of which might cause EDS (Roth & Roehrs, 1996).

d) Pupillography/Pupillometry

Until 1993 there was a rather limited use of pupillography because of mainly technical problems. But as video pupillography became available the possibility of image processing became the appropriate tool to use (Sitaram et al., 1983; Wilhelm et al., 1998). The pioneers in recording pupil activity in total darkness during alertness and fatigue were Lowenstein et al (1963), who described the 'fatigue waves'. 'Fatigue waves' are slow rhythmic changes of pupillary diameter that occur in complete darkness in subjects who are obviously sleepy. According to Yoss et al (1969, 1970), as the subject becomes sleepier, the pupil becomes smaller and starts to oscillate at a higher amplitude and slower frequency. Pupillary unrest index (PUI) is a measure of pupillomotor instability in darkness (Van Alpen, 1976).

Pupillography proves to be a fast and relatively simple method for gathering objective data about subject's wakefulness. Pupillography is also a very important tool in diagnosis, determining whether a patient really suffers from induced daytime sleepiness, and in therapy, assessing whether a therapy is successful or not. Moreover the test is significant for industrial medicine, advising a patient about his/her ability to drive a car or fulfil the demands of a job where falling asleep could become dangerous, and for social medicine, giving an objective opinion on the patient's ability to go back to work (Wilhelm et al., 1998).

Thus, both pupil oscillations and size in darkness and could play an important role in measuring sleepiness. The Pupil Sleepiness Test (PST) is new technique for the objective measurement of physiologic sleepiness, which is produced after sleep loss or sleep

fragmentation. In this test, fluctuations of the pupil and pupil diameter in darkness are considered as objective measures of physiologic or pathologic somnolence. But, still assessment of sleepiness requires examination times of at least 10 minutes that involves many difficulties (such as droopy eye lids, blinks, eye movements and corneal drying), especially in drowsy subjects.

The instruments that measure sleepiness subjectively are:

a) The Epworth Sleepiness Scale, ESS (Modafinil in Narcolepsy Multicenter Study Group, 1998)

ESS is a subjective self-administered questionnaire, which is designed to evaluate the general level of sleepiness. It asks the subjects to rate on a four point scale their chances of dozing in each of eight different situations of every day life (see appendix) (Johns, 1991, 1994). The test varies from value 0 to 24 and provides a measurement of the subject's sleep propensity in daily life (Johns, 2000). It is thought to be the most discriminating test of average sleep propensity (Johns, 1991).

b) Stanford Sleepiness Scale (SSS)

The SSS is a subjective assessment of alertness (Herscovitch & Broughton, 1991) - also known as fatigue and vigour scale - that measures the current degree of consciousness. It is a seven point scale (1= feeling active vital, alert – 7= no longer fighting sleep, sleep onset soon, having dream-like thoughts), widely used in sleep investigations, but unreliable when used in patients with chronic EDS (Guilleminault, 1994).

c) The Sleep-Wake Activity Inventory (SWAI)

SWAI is a multidimensional self-report test with an EDS scale designed to evaluate sleepiness apart from the influence of motivational and physic distress factors. It was first developed and validated relative to the MSLT. In this test the subject is asked to rate the likelihood of falling asleep in various different situations during the day. It assesses an important correlation between daytime sleepiness and difficulty of falling asleep at night or nocturnal sleep onset (Rosental et al., 1993b). SWAI is thought to be a potentially useful diagnostic threshold for self-reporting excessive daytime sleepiness (Johnson et al., 1999).

Syndromes and Causes of Sleepiness

- Quantitative Sleep Deficiencies

The most common cause of daytime sleepiness is insufficient nocturnal sleep. Although the recommended everyday sleep is about 8 hours, there is a variation in sleep need among individuals (Guilleminault & Brooks, 2001). Quantitative sleep deficiencies (sleep fragmentation, insufficient nocturnal sleep) are related to working late shift, lifestyle decisions or pathology (Rosenthal et al., 1993). The amount of nocturnal sleep is negative correlated to the degree of daytime sleepiness (Roehrs et al., 1989).

- Qualitative Sleep Deficiencies

Continuity in sleep is a very important factor for normal sleep. Sleep may be fragmented by brief arousal episodes (Guilleminault & Brooks, 2001) of 3-15 seconds that are usually not remembered by the patient (Roth et al., 1994). Sleep-related breathing disorders represent a very common cause of sleep fragmentation, and hence, daytime sleepiness. These disorders are mainly a consequence of abnormal anatomy superimposed on normal sleep physiology. During inspiration, pressure in the airway becomes negative relative to atmospheric pressure. If the airway pressure reaches a certain threshold (especially after sleep onset, when muscle tone diminishes and soft tissues of the airway become more compliant), complete or partial airway collapse occurs (Guilleminault & Brooks, 2001). Problems in sleep quality are usually the consequence of many deficiencies.

a) Sleep apnea (SA) is the most common diagnosis of patients with excessive daytime sleepiness in US Sleep Disorders Centers (Coleman et al, 1982). It is a serious, chronic disorder characterized by repeated episodes of partial or complete collapse of the upper airway during sleep (Guilleminault & Brooks, 2001). Specifically, collapse of the upper airway leads to episodes of cessation of breathing, which last for≥10 seconds and causes blood oxygen desaturation and sleep fragmentation (Guilleminault & Brooks, 2001) and finally leads to arousals. These arousals provide insufficient and unrefreshing sleep, which later produces EDS. Sleep apneic patients with EDS show positive correlation between total number of arousals and daytime sleepiness (Stepanski et al., 1984).

There are three main different types of sleep apneas:

i) Central sleep apnea, where breathing efforts cease or become minimal during each apnea.

ii) Obstructive sleep apnea (OSA), which is the most common type of sleep apneas. In OSA respiratory efforts persist during apneic periods and become unusually prominent. Each episode ends with an arousal.

iii) Mixed sleep apnea, which have characteristics of obstructive and central sleep apnea (Caplan et al., 2000; Vgontzas & Kales, 1999)

Obstructive Sleep Apnea/Hypopnea Syndrome (OSA/HS) is a sleep disorder that affects about 2-4% of middle-aged adults (Young et al., 1993) and tends to increase with age (Bixler et al, 1998). Periodic obstructions of the upper airway deteriorate sleep and, finally, lead to daytime sleepiness and impaired cognitive performance (Engleman et al., 1994; Dement et al., 1994). OSA/HS is associated with impairments in neurophysiologic, respiratory, cardiovascular and cerebrovascular function, causing increased mortality (Kales et al., 1985; Hung et al., 1990; Partinen & Guilleminault, 1990; Lavie et al, 1995) or diminished quality of life (D' Ambrosio et al., 1999; Yang et al., 2000). It is also an increased factor for occupational (Ulfberg et al., 2000) and automobile accidents (Barbe et al., 1998). Risk factors for OSA/HS syndrome include obesity, male sex, older age, craniofacial abnormalities or genetic and environmental factors (Riley et al., 1995).

Patients with OSA/HS are characterized by excessive daytime sleepiness, sleep attacks and repetitive nocturnal breath cessations followed by brief arousals. Many of them also show excessive body movements during sleep, diaphoresis, early morning headaches, secondary enuresis and sexual impotence. Familial predisposition is considered to be the main origin of sleep apnea (Vgontzas & Kales, 1999).

b) Periodic Limb Movements of sleep represent another very common cause of sleep fragmentation. It is characterized by repetitive involuntary movements of the limbs (usually the legs) during sleep. These movements fragment sleep and impact negatively daytime function (Guilleminault & Brooks, 2001).

c) Sleep quality can also be affected by a variety of medical conditions, such as arthritis, fibromyalgia, spondylosis, chronic pain, nocturnal angina, epilepsy, asthma,

chronic distractive pulmonary disease, alcoholism, urinary dysfunction, gastrointestinal disorders etc.

- Central Nervous System (CNS) pathologic abnormalities

a) Narcolepsy is an idiopathic CNS disorder that causes significant adverse effects on health related quality of life (Beusterien et al., 1999), such as excessive daytime sleepiness (Mitler et al., 1994), cataplexy (sudden loss of muscle tone), hypnagogic hallucinations, sleep paralysis (Williams et al., 1995), pathologic pattern of REM sleep (Guilleminault, 1994) and disrupted nocturnal sleep (Guilleminault & Brooks, 2001). Onset symptoms usually occur in adolescence (Guilleminault & Brooks, 2001). Although narcolepsy is of unknown origin it seems to have hereditary characteristics. Neuroanatomic degeneration and abnormal neurotransmitter function may also be involved in its creation. Several observations suggest that impaired catecholamine transmission may be responsible for EDS in narcolepsy (Baker & Dement, 1985; Boivin & Montplaisir, 1991; Mamelak, 1991) and other studies refer specifically to impairment of central-dopamine transmission (Montplaisir et al., 1982; Aldrich et al., 1992; Kish et al., 1992). For narcoleptic patients sleep attacks (brief episodes of sleep that may occur many times a day) and EDS are the most disabling aspects of the disorder (Montplaisir & Godbout, 1986).

b) Less common than narcolepsy, idiopathic CNS hypersomnia also causes EDS (Honda et al., 1983; Mignot et al., 1995) and impaired performance (Siegel et al., 1995) but without cataplexy or nocturnal sleep disruption. It is characterized as the disorder of excessive diurnal and nocturnal sleep, with increased total sleep time and naps that are usually not refreshing (Vgontzas & Kales, 1999). Its origin is still unknown, though several studies have shown a familial incidence (Vgontzas & Kales, 1999; Guilleminault & Brooks, 2001). The onset of its symptoms usually occurs in adolescence or in early adulthood (Guilleminault & Brooks, 2001).

c) Kleine-Levin syndrome is characterized by periodic hypersomnolence and episodes of EDS and occurs primarily in adolescents (Guilleminault & Brooks, 2001). Other characteristics of this syndrome are hyperphagia, aggressiveness, hallucinations and sexual hyperactivity (Weitzman & Fry, 1989), which last from days to weeks and are separated by weeks or months. Its origin is yet unknown (Guilleminault & Brooks, 2001).

- Circadian Disorders

The normal circadian cycle is the main regulator of alertness and sleepiness across the 24-h period (Turek, 2000). Circadian disorders are misalignments of the body's circadian rhythms with the environment (Graeber, 1994). If this physiological cycle is desynchronized, EDS may be experienced (Guilleminault & Brooks, 2001). Jet lag is a desynchronization of the individual with the environment (Graeber, 1994) while in shift work the circadian rhythms of the worker are out of phase (Monk, 1994).

- Nervous System Disorders

Somnolence can also occur after structural brain lesions, including strokes, tumours, haematomas, vascular malformations and multiple sclerosis or after encephalitis and head trauma (Guilleminault & Brooks, 2001). Sleep disruption and EDS are also common in many neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease and other dementias and multiple system atrophy (Askenasy, 1993; Chokroverty, 1996; Trenkwalder, 1998).

- Psychiatric Disorders

Psychiatric disorders are often associated with disrupted sleep. Especially in depression most of the patients suffer not only from insomnia, but excessive daytime sleepiness as well (Guilleminault & Brooks, 2001). There are also patients who suffer from 'psychogenic hypersomnia'. Such patients develop symptoms of excessive somnolence after a prolonged period of stress or following a period of disrupted sleep (Vgontzas et al., 2000).

- Drugs

Various drugs can cause excessive daytime sleepiness by reducing sleep latency, including sedatives, hypnotics, anxiolytics, antihistamines, anticonvulsants, antihypertensives, antidepressants and narcoleptics. It is also important that some drug-drug interactions or metabolic derangements (e.g. liver disease) may produce EDS (Guilleminault & Brooks, 2001).

Consequences of Excessive Daytime Sleepiness

The fact that patients who suffer from EDS also face many other disturbances-consequences of the disorder, drove to the creation of the 'Functional Outcomes of Sleep Questionnaire' (FOSQ). It is usually used in patients with EDS to assess daytime function and, in general, quality of life. It is a 30-item, self-administered questionnaire designed to assess the impact of disorders of EDS on five domains of everyday life: activity level, vigilance, intimacy, general productivity and social outcome (Schwartz et al., 2003).

The consequences of EDS may be far beyond the patients' sleep-wake cycle (Roth & Roehrs, 1996). The most significant of them are the following:

- Excessive sleepiness has a significant influence on psychosocial functioning. Specifically, patients are usually perceived by others as lazy or having psychological problems (Broughton et al., 1981). Also, their sleepiness forces them to face disruptions in family life and interpersonal relationships (Alaia et al., 1992; Roth et al., 1994). Perhaps related to the above, clinical depression is frequently observed in EDS patients (Broughton et al., 1981; Roth et al., 1994).
- Excessive somnolence has also been found to cause neuropsychological deficits, such as learning disabilities in children (Navelet et al., 1976) and memory impairments and reduced cognitive functions in children, adolescents and adults (Bedard et al., 1991). These deficits are caused by the impairment of daytime vigilance (Bedard et al., 1991).
- According to the National Commission of Sleep Disorders Research (1993), EDS is a major cause of accidents and death in modern society. For example, acute, rather than chronic, daytime sleepiness may be responsible for many motor vehicle accidents in general population (Roth & Roehrs, 1996). Moreover, vehicular and occupational accidents (Broughton et al., 1981) caused by EDS have even economic and public health ramifications (Leger, 1994; Webb, 1995).
- Patients with EDS often show reduced productivity both at work and school because of their inability to stay alert during the day (Roth et al., 1994).
- OSA patients with daytime somnolence usually suffer from systemic hypertension, dysregulation of glucose metabolism, weight gain and persistent cardiac dysrhythmias (Vgontzas & Kales, 1999).

Management of Excessive Daytime Sleepiness

Treatment of sleepiness varies depending on what causes it, severity of somnolence and its consequences on everyday function and quality of life.

a) Surgical Treatment

Specifically for the therapy of OSA/HS surgical options are often proposed, which include tracheostomy, uvulopalatopharyngoplasty and maxillofacial procedures (Riley et al., 1995).

b) Behavioural Treatment

Behavioural changes as a treatment for daytime sleepiness include weight loss and avoidance of alcohol for patients with OSA/HS (Engleman et al., 1998, 1999; Jenkinson et al., 1999; Kingshott et al., 2000). Patients with circadian disorders are suggested to have an entrainment to their new sleep-wake cycle, behaviourally, pharmacologically or both (Roth & Roehrs, 1996). Also, therapeutic naps enhance daytime alertness and reduce the need for high doses of stimulants as concerns patients with narcolepsy.

c) 'nasal Continuous Positive Airway Pressure' (nCPAP) (Riley et al., 1995)

nCPAP therapy is the treatment of choice in the management of patients with clinically significant OSA/HS. When used properly, nCPAP effectively manages apneas and hypopneas, eliminates oxygen desaturation, decreases sleep fragmentation and improves sleep quality, alertness, mood, cognitive function and quality of life (Pack et al., 2001). Various studies have indicated that nCPAP significantly improves self-reported (Engleman et al., 1998, 1999; Jenkinson et al., 1999; Kingshott et al., 2000) and objectively assessed daytime sleepiness (Lamphere et al., 1989; Sforza & Krieger, 1992; Engleman et al., 1994, 1998, 1999; Jenkinson et al, 1999; Kingshott et al., 2000) in patients with OSA/HS. Nevertheless, the mean level of sleepiness does not return to normal levels (Engleman et al., 1998, 1999; Jenkinson et al., 1999; Kingshott et al., 2000) and, in some cases, patients continue to complain of excessive daytime sleepiness, poor concentration and decreased quality of life, despite regular nCPAP use (Sforza & Krieger, 1992; Engleman et al., 1994; Kingshott et al., 2000, 2001).

d) Drug treatment

Treatment of narcolepsy-related sleepiness and sleepiness caused by idiopathic hypersomnia (Roth & Roehrs, 1996) employs amphetamine and amphetamine-like CNS stimulant drugs (Vgontzas & Kales, 1999), such as methylphenidate, dextroamphetamine pemoline (Guilleminault, 1994; Mitler et al., 1994). Stimulants primarily reduce sleepiness by increasing catecholaminergic - particularly adrenergic - activity. Studies in mice with deletion of the dopamine transporter gene indicate that the dopamine transporter is necessary for the wake-promoting effect of modafinil and amphetamines (Wisor et al., 2001). Also, increased dopaminergic transmission appears to mediate the wake-promoting effects of modafinil in patients with narcolepsy (Broughton et al., 1997; Modafinil in Narcolepsy Multicenter Study Group, 1998), treated sleep apnea (Pack et al., 2001) and sleep deprived volunteers (Wesenten et al., 2002). Drug treatment of patients with excessive daytime somnolence includes caffeine, amphetamines, pemoline, methylphenidate and modafinil.

1. Caffeine, chemically, is a trimethylxanthine, which appears to enhance catecholaminergic function indirectly via antagonism of adenosine (Roth & Roehrs, 1996). It is very effective in postponing sleep and decreasing fatigue in boring and repetitive tasks (Dews, 1984), although effects of caffeine on daytime performance in the alert individuals are still unclear (Kuznicki & Turner, 1986; Lieberman et al., 1987). In sleep-deprived subjects moderate doses of caffeine have been found to cause a significant alerting effect for 5-6 hours after administration (Penatar & Thorne, 1990; Rosenthal et al., 1991). But repeated consumption can cause decrease in hand steadiness (Dews, 1984) and increase in tension and anxiety (Bonnet & Arand, 1990a, 1990b).
2. D-amphetamine exerts most of its effects in the CNS by releasing biogenic amines from nerve terminals (main action of noradrenaline or dopamine) (Weiner, 1985; Rambert et al., 1990). It causes vigilance enhancement in alert normal subjects (Smith, 1992) and in sleep-deprived subjects as well (Newhouse, 1989; Pigeau et al., 1995), but also decreases total sleep time due to the decrease of total REM time (dose-response relationship) (Penatar et al., 1990). The hyperactivity

which is induced by dexamphetamine depends on its internalization by dopamine neurons owing to the dopamine carrier. This triggers the release of dopamine, thus inverting the way of the dopamine neuronal transport (Kamal et al, 1981). Furthermore, d-amphetamine disturbs sleep continuity with an increased number of awakenings and movements during sleep (Saletu et al., 1989). Dexamphetamine also affects decision making and psychomotor performance by provoking euphoria, agitation, restlessness and sometimes toxic psychosis (Davis, 1974). It also causes extremely high abuse potential and other side effects, such as hypertension, tachycardia, anorexia, anxiety (Simon et al., 1994) and 'amphetaminic psychosis' (Kamal et al, 1981).

3. Pemoline is an oxizolidine which is slowly absorbed in the gastrointestinal tract, because of its poor aqueous and lipid solubility (Vermeulen et al., 1979). Past studies have shown its efficacy in the treatment of narcolepsy, as it causes lengthened daytime sleep latencies and improved attention and increased wakefulness during nocturnal sleep (Mitler & Hajdukovic, 1991; Sangal & Thomas, 1994). Side effects and toxic consequences of pemoline in adults still remain an unexplored issue (Badkoff et al., 1991), whereas studies on children and adolescents have shown a high incidence of abnormal involuntary movements (Sallee et al., 1989).
4. Methylphenidate is the preferred drug for treating sleep attacks because of its fast onset of action and relatively few side effects in narcoleptic patients (Vgontzas & Kales, 1999).

Most CNS stimulants are often associated with side effects and cause CNS cardiovascular or gastrointestinal adverse experiences (e.g. anxiety, palpitation, nausea) (Hoffman & Lefkowitz, 1996; O'Brien, 1996). They are also associated with a significant abuse potential in the general population (Mitler et al., 2000). For that reason they are not effective in long-term treatment (Hoffman & Lefkowitz, 1996; O'Brien, 1996).

5. Modafinil is a new compound that appears to be as effective as the classical stimulants with the advantage of minimal adverse effects (Roth & Roehrs, 1996; Vgontzas & Kales, 1999). It is a putative a_1- postsynaptic agonist with alerting properties (Duteil et al., 1979, 1990; Akaoka et al., 1991; Lin et al., 1991) in treating human narcolepsy (Billiard et al., 1994; Laffont et al., 1994) and idiopathic hypersomnia (Billiard et al., 1987; Laffont et al., 1987; Bastuji & Jouvet, 1988; Billiard et al., 1991, 1994; Marchand et al., 1991). In subjects without excessive somnolence it has been proved to help for maintaining or recovering performance during prolonged sleep loss or continuous work (Buguet et al., 1995; Pigeau et al, 1995).

Ib. Modafinil, [(diphenylmethyl-sulphinyl)] 2-acetamide

Pharmacological Profile of Modafinil

Modafinil (CRL 40476) is a new drug, which was first discovered and developed in France since 1982 by Laboratoire L. Lafon, for the treatment of narcolepsy. It has been commercially available in France since late 1994 (Laffont, 1996; Moachon et al, 1996). It represents the development of the already known adrafinil (one of its metabolites) (Rambert et al., 1993). Its mechanism of action appears to be connected to the central a_1-adrenoreceptor stimulation (Duteil et al., 1990). In humans, modafinil exhibits linear kinetics, with dose-dependent increase in plasma concentrations, after either single or repeated administration. It is extensively metabolized and its main metabolites are modafinil acid (CRL 40467), modafinil sulfone (CRL 41056), the hydroxylated derivative CRL 41977 and peak A. The percentage of unchanged modafinil excreted in the urine is low (<10% of the administered dose). Pharmacokinetics of modafinil is not modified by food but altered in patients with severe hepatic and renal disease (Moachon et al., 1996). The drug has 1-4 hour peak serum concentration after oral administration and approximately 10-13 hours half-life (Civil et al., 1995). The most frequently used dosage range is 200-400mg per day (either as two divided doses in the morning and at noon or as a single morning dose), but up to 600mg per day is safe (Lagarde & Batejat, 1995; Buguet et al., 1995).

Modafinil (Modiodal) is a new putative postsynaptic potentiator, a non amphetaminic vigilance-enhancing drug. It has been found to increase wakefulness and brain temperature in a dose-dependent manner and parallel to amphetamines (Lin et al., 1992). Just like amphetamines, it has been shown to successfully treat narcolepsy-cataplexy and idiopathic hypersomnia (Simon et al., 1995). However, a number of studies demonstrate that modafinil is reliably discriminated from other stimulants such as cocaine, amphetamines and methylphenidate (Jasinski & Kovacevic-Ristanovic, 2000; Jasinski, 2000; Rush et al., 2002a, 2002b).

Although it has wake-promoting actions common to traditional CNS stimulants, it is chemically dissimilar to and with a different pharmacologic profile from them (Jasinski

& Kovacevic-Ristanovic, 2000; Mitler et al., 2000). Animal studies have shown that modafinil interacts with a wide variety of neurotransmitter and neuropeptide pathways (monoaminergic, glutamatergic, gabaergic, orexinergic) (Tanganelli et al., 1995; Ferraro et al., 1996; Nishino & Mignot, 1997; Scammel et al., 2000), while amphetamines act via monoaminergic mechanisms, preferentially stimulating norepinephrine and dopamine release. While both amphetamines and modafinil promote vigilance and arousal, only amphetamine-induced arousal is associated with marked signs of behavioural excitation, toxicity, tolerance or significant sleep disturbances (Saletu et al., 1989; Buguet et al, 1995).

Traditional stimulants appear to promote wakefulness by facilitating neural transmission through catecholamines, particularly dopamine (Perez de la Mora et al., 1999). Specifically, amphetamines act presynaptically on catecholaminergic nerve terminals to enhance the release and probably to prevent the reuptake of dopamine, which may activate its own target receptors to enhance wakefulness and behavioural activity. Studies have shown that treatment with a-methyl-p-tyrosine (aMPT), a catecholamine synthesis inhibitor, almost completely prevented the effects of amphetamine and the dopamine D_1/D_2 antagonist haloperidol blocked significantly the arousal and locomotor activity caused by amphetamines (Lin et al., 1992), while pre-treatment or single administration caused only slight or no changes on locomotor activity and arousal caused by modafinil (Duteil et al., 1990; Lin et al., 1992). Modafinil-induced (in a single administration) increase in locomotor activity in mice was also not prevented by the dopamine D_2 antagonist sulpiride, the peripherally acting a_1- adrenoreceptor antagonist phentolamine, the a_2- adrenoreceptor antagonist yohimbine and the b- adrenoreceptor antagonist propranohol (Duteil et al., 1990). On the other hand, pre-treatment with phentolamine, a peripherally acting a_1- adrenoreceptor antagonist, or prazosin, a centrally acting a_1- adrenoreceptor antagonist, or propranohol, a b- adrenoreceptor antagonist, attenuated significantly the arousal effect of modafinil, but not of amphetamine (Lin et al., 1992). The locomotor effect of modafinil was prevented after single administration with the centrally acting a_1-adrenoreceptor antagonists, prazosin and phenoxybenzamine, and by reserpine (Duteil et al., 1990). Finally, the effects of both drugs were increased after pre-treatment with yohimbine, an a_2- and b- adrenoreceptor antagonist (Lin et al.,

1992). Thus, the awaking effect of modafinil does not appear to depend on the availability of endogenous catecholamines but might result from an enhancement of postsynaptic a_1- and b- receptor activity (Lin et al., 1992). There is a prominent role of noradrenaline and intact central postsynaptic a_1-adrenoreceptors for the development of locomotor activity in mice and nocturnal awakening in monkeys. However, the absence of peripheral sympathetic effects (no salivation, no contraction of the pupil dilator muscle, and slight mydriasis in higher doses) is noteworthy (Duteil et al., 1990).

Moreover, traditional stimulants have been found to induce hyperactivity in animals, which is usually followed by stereotyped behaviour. Animal studies have shown that haloperidol antagonizes the stimulant effect of amphetamine, the D_1 dopamine receptor antagonist SCH 23390 reverses the amphetamine induced hyperactivity and the a-methyl-p-tyrosine suppresses the hyperactivity induced by dexamphetamine. A single treatment with L-DOPA, which induces repletion of the dopamine stores, has been shown to enhance the amphetamine but not modafinil effect on the climbing behaviour (stereotype behaviour). Treatment with resperine, which causes depletion of the vesicular store of the monoamines (dopamine, noradrenaline and serotonin), results in complete akinesia, which can be reversed by amphetamine, but not by modafinil. Thus, the modafinil induced stimulant locomotor effect differs completely from that of amphetamines (Simon et al., 1995).

Studies have also indicated distinct regional activation after equal wake-promoting doses of amphetamine, methylphenidate and modafinil. Amphetamine and methylphenidate increase activity throughout the brain (Milhaud & Lagarde, 1988). They induce activity mostly in the striatum, especially the caudate nucleus, which receives projections from mesencephalic dopaminergic neurons, and in various cortical areas, specifically the mediofrontal cortex, which is a significant cortical target of mesoneocortical system originating from the dopaminergic ventral tegmental area (VTA). Through activation of the striatum and cortex dopaminergic targets both amphetamine and methylphenidate are involved in the control of awakening, drug tolerance and dependency (Lin et al., 1996). On the other hand, modafinil not only produces activity mainly in subcortical brain areas but also causes paucity of cortical activation, which suggests that its awakening property cannot be explained in terms of direct

pharmacological cortical activation, as occurs with the two dopaminergic agents (Milhaud & Lagarde, 1988; Lin et al., 1996). Modafinil has been indicated to produce activation of the anterior hypothalamic area (AHA) and the adjacent suprachiasmatic nucleus (SCN). AHA may serve as a key target for the waking effect of modafinil due to its spatial anatomical disposition. It is situated between the preoptic area, which plays an essential role in sleep generation, and the posterior hypothalamus, in which histaminergic neurons [exclusively located to the tuberomammillary nucleus (TMN) in the posterior lateral hypothalamus] constitute an important component for arousal, making numerous reciprocal connections with both (Lin et al., 1996). Specifically, modafinil strongly activates TMN (histamine-containing neurons) and orexin-A neurons which are exclusively localized in the lateral hypothalamic area, implicated in the regulation of wakefulness as well (Chemelli et al., 1999; Huang et al., 2001; Tashiro et al., 2002). These cell groups are anatomically well-positioned to facilitate wakefulness with ascending excitatory histaminergic projections to the cortex, basal forebrain and middle thalamus and descending excitatory projections to dorsal raphe nucleus, locus coeruleus (LC) and pontine cholinergic region (Scammel et al., 2000).

The precise actions of modafinil are unknown. One of the main neurochemical mechanisms underlying the wakefulness action of modafinil may be related to a reduction of GABAergic transmission in sleep and non-sleep-related brain areas (Tanganelli et al., 1992, 1995; Ferraro et al., 1996). It has been already shown that the vigilance promoting action of modafinil is related to an inhibitory effect of the drug on GABA release in the Cerebral Cortex (CC) (Tanganelli et al., 1992; Lin et al., 1996). Also, the dopamine releasing action of modafinil in the nucleus accumbens (Nac) is produced due to its ability to reduce local GABAergic transmission, which leads to reduction of $GABA_A$ receptor signalling on the dopamine terminals (Ferraro et al., 1996a). The ability of modafinil to enhance alertness may also be related to a reduction of GABAergic transmission mostly in medial preoptic area (MPA) and less in posterior hypothalamus (PH), through the activation of local serotonergic terminal systems. These areas are known to play an important role in the regulation of sleep (Ferraro et al., 1996b).

Modafinil has been shown to dose-dependently increase glutamate (Glu) release in the ventromedial thalamus (VMT) and the ventrolateral thalamus (VLT), whereas only

at a higher dose increases glutamate release in Hippocampal formation (Hip). However, the drug causes GABA decrease in VMT only at 300mg/kg dose, with a short-lasting decrease in VLT and weak effects in Hip. Thus, it seems that modafinil may increase excitatory glutamatergic transmission in these regions, altering the balance between glutamate and GABA transmission (Ferraro et al., 1997).

Modafinil through cortical noradrenergic neurons exert its 5-HT mediated inhibition of GABA release in the cerebral cortex (Tanganelli et al., 1994, 1995). So, the drug, by acting on noradrenergic system indirectly, activates inhibitory 5-HT neuronal systems leading to the reduction in cortical GABA outflow. These results also suggest that possibly the arousal effect of modafinil does not depend on the availability of endogenous catecholamines but result rather from an indirect enhancement for a_1- and b-receptor activity, in which the adrenergic system may play a 'permissive' role in the actions of modafinil (Rush et al., 2002a). The catecholaminergic stimulation caused by modafinil seems to be exerted at the postsynaptic level, whereas amphetamines have presynaptic action (Lin et al., 1992). Nevertheless, it has been indicated that dopamine transporters play an important role in sleep regulation and are necessary for the specific wake-promoting actions of both amphetamines and modafinil (Wisor et al., 2001).

Due to the fact that modafinil is chemically and pharmacologically unrelated to CNS stimulants (methylphenidate, amphetamines, pemoline), it has an excellent safety profile, both for healthy volunteers and narcoleptic or hypersomniac patients and causes fewer side effects (Billiard et al., 1994) and little evidence for dependence (Jasinski, 2000) than other conventional stimulants. Modafinil is associated with a low potential for abuse, tolerance or dependence and increase in locomotor activity only in proportion to the amount that is expected because of increased time awake (Bastuji & Jouvet, 1988; Lyons & French, 1991; Lin et al., 1996). It has also no apparent adverse effects on night sleep (Littner et al., 2001), as its sleep characteristics and nocturnal sleep organization remain unaffected, after three or even seven years of treatment (Bastuji & Jouvet, 1988; Boivin et al., 1993; Pigeau et al., 1995). Modafinil is effective against somnolence without increasing subsequent sleep or causing 'rebound hypersomnolence', which presents a very serious safety concern, especially for individuals operating motor vehicles or performing other hazardous functions (Edgar & Seidel, 1997).

Today, modafinil is considered to be an alternative to 'gold-standard' stimulants, such as d-amphetamine, precisely because it is not addictive and exhibits far fewer negative side effects. The ability of modafinil to induce wakefulness without producing behavioural disturbances or a subsequent sleep rebound makes it a promising tool in the therapeutics of insomnia and excessive daytime sleepiness and in sleep-wake research (Lin et al., 1992).

Other potential therapeutic effects of Modafinil

Modafinil showed statistically significant improvements as a treatment for children with Attention Deficit/Hyperactivity Disorder (ADHD) and a very low incidence of side effects (Rugino & Copley, 2001). After treatment with the drug, children with ADHD have shown reductions in hyperactivity, inattention and impulsivity (Rugino & Copley, 2001; Rugino & Samsock, 2003).

Modafinil is also thought to protect against neurotoxicity and striatal ischemia. It seems to be a promising pharmacological approach for Parkinson's disease (PD), with a potential antiparkinsonian and neuroprotective role (Jenner et al., 2000). In addition, modafinil reduces sleepiness and fatigue in PD (Nieves & Lang, 2002) and in depression (Menza et al., 2000).

Modafinil is also thought to represent an important addition on the pharmacological treatments for management of multiple sclerosis related fatigue (Rammohan et al., 2002) and myotonic dystrophy related hypersomnolence (MacDonald et al., 2002).

Modafinil, Daytime Sleepiness and Cognitive Performance

Modafinil has gained attention for its apparent selectivity in promoting alertness and its potentiality for treating EDS (Bastuji & Jouvet, 1988; Lagarde & Milhaud, 1990; Boivin et al., 1993)) with less peripheral or central side effects (Buguet et al., 1995; Simon et al., 1994) and abuse liability than amphetamines (Gold & Balster, 1996). Many studies have shown that modafinil increases arousal levels in normal animals (Milhaud &

Lagarde, 1988; Duteil et al., 1990; Lagarde & Milhaud, 1990; Rambert et al., 1990; Hermant et al., 1991; Lin et al., 1992; Simon et al., 1994, 1995; Touret et al., 1995). Specifically, it has been found to produce a markedly increase of locomotor activity in mice and rats and nocturnal activity in monkeys (Duteil et al., 1990; Hermant et al., 1991) and to improve wakefulness in monkeys (Lagarde & Milhaud, 1990).

Modafinil has been found to increase wakefulness in humans as well (Duteil et al., 1979; Saletu et al., 1989; Boivin & Montplaisir, 1991; Lyons & French, 1991; Mitler & Hajdukovic, 1991; Billiard et al., 1994; Laffont et al., 1994; Homeyer et al., 1995; Lagarde et al., 1995). Measures with EEG indicate that in non sleep deprived subjects, whether they are young or elderly (Goldenberg & Weil, 1986; Saletu et al., 1986), it sustains alertness (Saletu et al., 1989; Lagarde et al., 1995; Caldwell et al., 2000). In narcoleptics, modafinil has been found to reduce daytime sleepiness (Besset et al., 1996) – even in a daily dose of 200mg (Broughton et al., 1997) - and improve cognitive performance (Boivin et al., 1993) and subjectively measured vigilance (Boivin et al., 1993). It is suggested that modafinil may have a part in therapeutic strategy of OSA/HS patients with residual EDS for non-users of nCPAP therapy (Arnulf et al., 1997) or for patients effectively treated with nCPAP therapy (Pack et al., 2001). Moreover, the drug is thought to be an effective treatment for EDS associated with narcolepsy (Bastuji & Jouvet 1988; Saletu et al., 1989; Boivin & Montplaisir, 1991; Lyons & French, 1991; Mitler & Hajdukovic, 1991; Billiard et al., 1994; Laffont et al., 1994; Broughton et al., 1997; Mitler et al., 1998; Modafinil in Narcolepsy Multicenter Study Group, 1998; Mitler et al., 2000; Modafinil in Narcolepsy Multicenter Study Group, 2000; Moldofsky et al., 2000) idiopathic hypersomnia (Bastuji & Jouvet, 1988; Laffont et al., 1994; Lagarde et al., 1995) and sleep deprivation (Buguet et al., 1995; Batejat & Lagarde, 1999; Caldwell et al., 2000). The characteristics of dose-related induction of wakefulness and the absence of behavioural disturbances promote modafinil as a promising tool for the treatment of EDS (Lin et al., 1992; Mitler et al., 2000) and pathological daytime somnolence (Modafinil in Narcolepsy Multicenter Study Group, 1998).

Modafinil offers significant potential as a cognitive enhancer especially on tasks that depend on spatial planning, memory, digit span and accuracy (Turner et al., 2003). Adults with ADHD after treatment with modafinil improved their performance on tests of

digit span, visual memory, spatial planning and decision making (Turner et al., 2004a). Modafinil also induced an improvement of short-term memory functions in patients with severe sleep apnea syndrome (Arnulf et al., 1997) and chronic alcoholics (Saletu et al., 1993). EEG analysis and functional magnetic resonance imaging studies have indicated that modafinil significantly modifies the activity of brain areas which are involved in learning processes and memory functions, such as hippocampus and prefrontal cortex (Winocur, 1992; Ellis et al., 1999; Seban et al., 1999). In patients with schizophrenia modafinil is associated with improvement on short term verbal memory span and attentional set shifting and slowed response latency on the spatial planning task (Turner et al., 2004b). In narcoleptics modafinil has been found to improve cognitive performance as well (Boivin et al., 1993). In sleep-deprivation studies, the drug has been shown to improve objective cognitive performance (Wesenten et al., 2002) and ameliorate the effects of sleep deprivation stress, especially on perceptual, judgement tasks, on complex mental tasks (Pigeau et al., 1995) and on reaction tasks (Baranski et al., 1997). However, studies in young individuals who are not sleep-deprived showed equivocal findings (Randal et al., 2003; Turner et al., 2003, Randal et al., 2004).

Modafinil and Side Effects

Modafinil has been reported to cause only mild side effects. The most important complaints refer to nausea, vertigo (Caldwell et al., 2000) and headache (Laffont et al., 1987). The drug may also cause hypersalivation (Laffont et al., 1987), moderate tachycardia (Goldenberg et al., 1987), nervousness (Moldofsky et al., 2000), gastralgia, hot flushes and dry mouth. The incidence of these negative effects is rather low and most of them disappear when doses are reduced (Laffont et al., 1999).

Furthermore, it has been shown that individuals who were sleep-deprived induced ‘overconfidence’ after their treatment with a high/normal dose of modafinil (Baranski et al., 1997). Other studies found no evidence of ‘overconfidence’ when the drug was administered in small doses throughout a period of sleep deprivation (Turner et al., 2004a) and in non-sleep deprived individuals though there was a non-significant trend towards mild overconfidence (Baranski et al., 2004).

Ic. The Human Pupil

Anatomy of the Iris

The iris is interposed between the anterior and posterior chambers of the eye and has a three dimensional shape. Its root is very thin and posteriorly it merges with the ciliary body, which surrounds the lens. The axial border rests lightly on the lens and forms a central aperture termed the pupil, which acts as a diaphragm to control the amount of light reaching the retina. The iris consists of two main parts: the posterior leaf, containing the iris muscles and the posterior pigment epithelium, and the mesodermal anterior stroma, a bulk of collagen fibres which carries the iris vessels nerves and chromatophores. The anterior border layer of the iris stroma (towards the cornea) is made up of denser tissue than its middle portion and contains more pigmented cells, especially in darker irides. The iris muscles are derived from neuroectoderm of the optic cup (Kandel et al., 2000) and their activity determines the size of the pupil (Merritt et al., 2004). The iris sphincter muscle is a thin (0.7-1mm) band of smooth muscle cells, forming a continuous ring around the pupillary margin. The dilator muscle is a radially arranged thin layer of primitive myoepithelial cells, stretching from the peripheral iris root to the area beneath the sphincter ring, within 0.3mm of the pupillary margin (Kandel et al., 2000).

Characteristics of the Human Iris

In human eyes the pupil can vary from less than 1mm to more than 9mm. It is easier for a large pupil to contract than it is for a pupil that is already small. Conversely, an already large pupil cannot dilate as freely as can a smaller pupil. The normal pupil has e linear range of movement. For most humans the lower end for linear contraction is around 3-3.5mm (floor) and the upper end for linear pupillary dilation is about 6mm (ceiling) (Loewenfeld, 1999).

Parasympathetic Innervation of the Iris

The pupillary light response is elicited by shining a bright light in one eye. The axons of retinal ganglion cells travel through the optic disc and then together form the bilateral optic nerves. Optic nerves from each eye project to the optic chiasm, where fibers from each eye destined for one or the other side of the brain are sorted out and rebundled in the bilateral optic tracts. The optic tracts project to three major subcortical areas: the pretectum (in the midbrain), the superior colliculus and the lateral geniculate nucleus (in the thalamus). The lateral geniculate nucleus processes visual information for perception, the superior colliculus contributes to saccadic eye movements and the pretectum of the midbrain controls the pupillary reflexes. Light shinning in one eye causes constriction of the pupil in that eye (direct response), as well as in the other eye (consensual response) (Kandel et al., 2000).

The 'W' or 'gamma' retinal ganglion cells, which are located in all areas of the retina, transmit information about light brightness by travelling in the optic nerves. The larger part of them crosses the optic chiasm, whereas some remain uncrossed, resulting in numerous ganglion cells in the temporal retina and sending axons to the ipsilateral optic tract. The pupillary afferents constitute almost 10% of all fibres in the optic tracts. Before reaching the lateral geniculate nucleus, they separate from the optic tract and run by way of the branchia of the superior colliculi to the rostrodorsal midbrain. They do not enter the colliculi, but pass mediorostrally to the pretectal area at the midbrain-diencephalon junction. There they synapse on the pretectal neurones of the pretectal nuclei (Sillito & Zbrozyna, 1970; Hultborn et al., 1978). The cells in the pretectal area then project bilaterally to preganglionic parasympathetic neurons in the Edinger-Westphal (or accessory oculomotor) nucleus of the oculomotor nucleus (cranial nerve III). Preganglionic neurons in the Edinger-Westphal nucleus send axons out of the brainstem in the oculomotor nerve to innervate the ciliary ganglion. This ganglion contains the postganglionic neurons that innervate the smooth muscle of the pupillary sphincter that constricts the pupil [see Figure 1 (Kandel et al., 2000)].

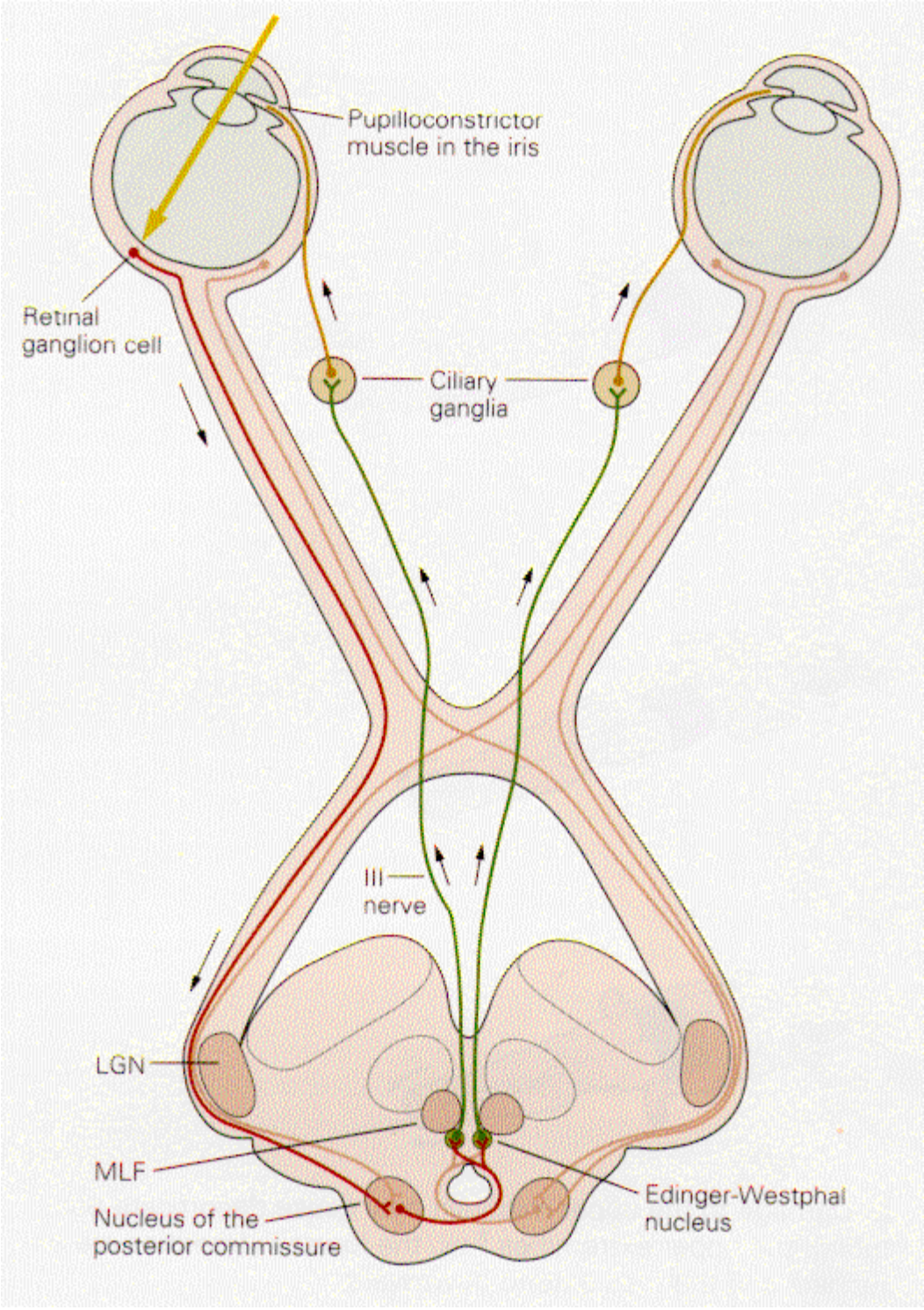


Figure 1. Parasympathetic innervation of the iris (Kandel et al., 2000)

Sympathetic Innervation of the Iris

From the hypothalamus in the diencephalon arise the great efferent sympathetic fibre system, which innervates all visceral organs of the body, a small part of which is the sympathetic pathway to the iris dilator muscle of the eye. It descends through the entire brainstem and cervical spinal cord and then again ascends in the neck, in the cervical sympathetic chain. It re-enters the skull and, associated with the fifth nerve, passes quite close to its hypothalamic origin toward the eye.

Three parts make up this path, the 'central neuron', from the hypothalamus to the cervicothoracic cord, the 'preganglionic neuron', from the cord to the superior cervical ganglion and the 'postganglionic neuron', from the superior cervical ganglion to the iris) (see Figure 2, Kandel et al., 2000). The first pathway originates from the hypothalamus and is probably under the control of noradrenergic nuclei of the lower brainstem (both areas A1/A5 and locus coeruleus) on the hypothalamus. From the hypothalamus, the central pupillodilator tract runs caudally via the subthalamic-prerubral area. In the cord, the fibres travel superficially in the lateral funiculus until at the C8 to T2 level they turn mesially and synapse with the preganglionic sympathetic neurons in the intermediolateral cell column ('Budge's centre'). The preganglionic pupillary sympathetic fibres arise from the lateral horn cells of the cervicothoracic spinal cord. They leave the cord by its ventral roots and after they join the sympathetic chain, they turn upward toward the head. They traverse the first thoracic and inferior cervical ganglia and then pass without interruption via the ansa of Vieussens, the middle cervical ganglion, near the bifurcation of the internal and external carotid arteries, where they synapse with the postganglionic neurones. Postganglionic fibres of the pupil leave the superior cervical ganglion at its rostral pole and join the carotid plexus, which is adjacent to the internal carotid artery, into its canal in the temporal bone. They approach the Gasserian ganglion and enter the ophthalmic branch of the trigeminal nerve just distal to its origin from that ganglion. After they run in the middle fossa they pass into the nasociliary branch of the fifth nerve and, after bypassing the ciliary ganglion, they reach the iris dilator muscle via the long ciliary fibres (Kerr & Brown, 1964; Koss & Wang, 1972; Loewy et al., 1973; Saper et al., 1976).

The two iris muscles, sphincter and dilator, can be viewed as an agonist-antagonist pair. Combined innervation of the agonist muscle and inhibition of the antagonist muscle produce much more sensitive and rapid response than the contraction of the agonist muscle itself. During the light reflex, contraction of the sphincter is accompanied by relaxation of the dilator muscle (Lefkowitz et al., 1990).

This agonist-antagonist pair also plays an important role in alertness or sleepiness. Parasympathetic pupilloconstrictor neurons in the midbrain area of the Edinger-Westphal nucleus fire continually and travel via parasympathetic reflex pathways to activate the sphincter muscle and constrict the pupil. Central influences (alertness, emotions) and the peripheral sympathetic branch activate the dilator muscle. In alert individuals, excitatory impulses arise from the cerebral cortex and travel through the reticular activating system and hypothalamus to cause pupil dilation by (a) inhibiting the EW nucleus and parasympathetic constrictor activity and (b) activating the peripheral sympathetic pathway to the dilator muscle (Moro et al., 1981). Progressive loss of central sympathetic influences is the basis for pupillary oscillations and miosis. With ensuing sleepiness, central and hypothalamic centers cease to function in an orderly manner, central inhibition of the EW nucleus decreases, sympathetic tone is steadily lost and a preponderance of parasympathetic activity occurs that is reflected in decreasing pupil size and large, slow pupillary oscillations (Hutchings & Holly Field, 1984).

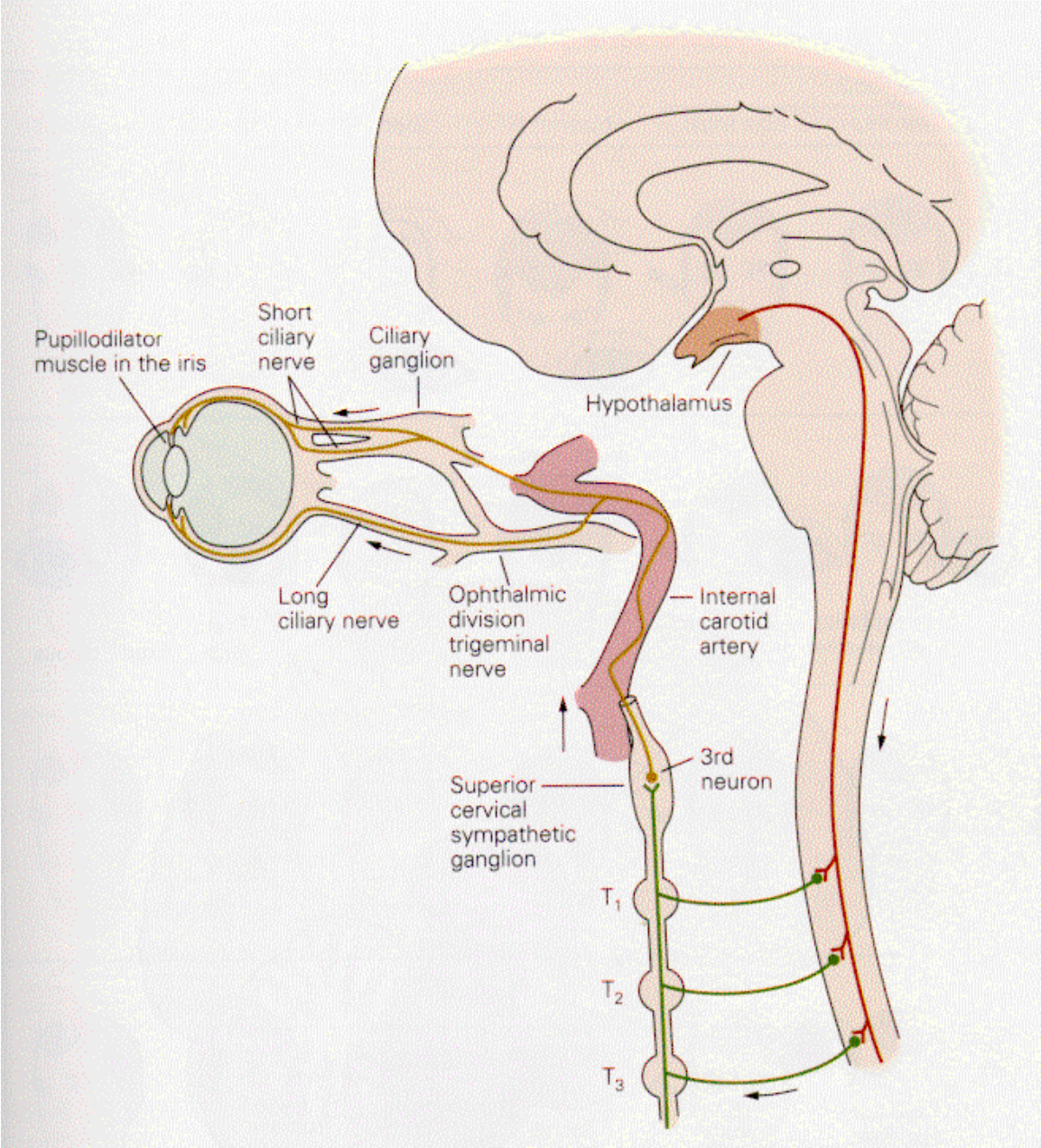


Figure 2. Sympathetic innervation of the iris (Kandel et al., 2000)

The Pupillary Reflex Characteristics

There are three main pupillary reflexes: the light reflex, the darkness reflex and the psychosensory reflex.

A) The pupillary light reflex

1. Stimulus intensity

The amplitude and the constriction velocity of the light reflex depend on the activity of neurones in the parasympathetic Edinger-Westphal nucleus. This activity is regulated by two factors: a) stimulus intensity and b) supranuclear inhibition of the Edinger-Westphal nucleus. The pupillary reaction to a weak flash activates very few neurons and has a long latent period, followed by a contraction that is slow, brief in duration and inextensive. In contrast, a very bright light causes a large number of neurons recruited in the Edinger-Westphal nucleus and, thus, can drive the pupils into tight miosis that may continue for several seconds. However, the number of recruited neurones as well as their firing rates can be attenuated proportionally to the amount of central supranuclear inhibition of the Edinger-Westphal nuclei.

2. Stimulus duration

When a moderately bright flash is short, the pupillary contraction is short as well and redilation follows immediately, resulting in a V-shaped response. When the flash is longer in duration, the contraction lasts for a longer time. However, the latent period and the peak speed are the same for reactions to short or longer-lasting stimuli of the same intensity.

When a bright light is left on continuously, the pupils contract fully for some time and then relax somewhat as the eyes adapt to the light. Weak, continuous light cannot maintain such a continued contraction.

In steady illumination pupils oscillate up and down continuously in irregular rhythm. The brighter is the light, the smaller and more frequent are these movements, while they slow down and become more extensive in dimmer illumination. The fluctuation continues as long as the light is left on, which is not pathologic and vary among individuals. These light-induced oscillations have been named ‘pupillary unrest’.

3. Stimulus wave and frequency

When short, bright light flashes are presented in rapid succession, the individual wavelets of pupillary contraction and redilation become smaller and smaller and the mean pupil size declines. Thus, the pupillary sphincter is driven into titanic contraction.

4. Onset Latency

The time that elapses between the onset of a light and the beginning of pupillary contraction is known as the latent period of the reflex. This period depends, firstly, on the quickness of the sphincter muscle, which sets the minimal latency and, second, on the intensity of the light stimulus, which determines the duration of an additional time delay, consumed by the retinal receptors and the neural reflex arc. The dimmer the light, or the smaller the retinal area stimulated, or the less-complete the previous dark-adaptation, or the more gradual the light onset and the less effective its colour, the longer will be the latent period of the reflex. In mammals the minimal latent period is in the 120 to 200msec range, and the additional delay for weak light is about 250msec (Loewenfeld, 1999).

5. Recovery (redilation) time

The decrease in pupil size in response to the onset of a light stimulus is followed by a redilation to initial levels in response to the offset of the stimulus. The redilation in response to light stimulus offset is largely dependent on intact sympathetic function of the hypothalamus and the peripheral sympathetic chain (Loewenfeld, 1999; Smith S.A., 1992). Redilation is faster at the beginning of the recovery phase, when the firing of Edinger-Westphal neurones decreases, until they stop (peak amplitude) and the central sympathetic system takes over (Smith S.A., 1992). Then the peripheral sympathetic input to the iris widens the pupil more slowly and the redilation velocity decreases. There are indications that the fast redilation phase solely reflects withdrawal of the parasympathetic tone that determines the rate of recovery of pupil size after a light stimulus (Loewenfeld, 1999; Heller et al., 1990; Smith S.A, 1992), whereas the slow redilation phase is a pure measure of peripheral sympathetic activity (Loewenfeld, 1999; Smith S.A, 1992).

B) The pupillary darkness reflex

The pupillary reaction to a short dark interval in eyes previously adapted to ambient light is called 'darkness reflex'. The dark period elicits pupillary dilation, preceded by a latent period slightly longer than that of a light reflex. After the light reappears the pupils contract below the previous light-adapted diameter and then redilate to baseline (triphasic response). The darkness-evoked dilation is due to: a) reduction of impulse traffic to the parasympathetically innervated pupillary sphincter, which affects both pupils and b) increased sympathetic discharges to the pupillary dilator, which can reach the intact iris only (Loewenfeld, 1999).

Darkness stimuli elicit retinal 'off' discharges, which are probably partly responsible for the dilation phase of the response, and reappearance of the light elicits retinal 'on' discharges, which are responsible for the secondary contraction-redilation movement (Loewenfeld, 1999).

The extensiveness of the darkness-evoked dilation is directly related to the intensity of the previously adapting light. When the light's intensity is reduced (or when the dark period is very short) the dilation has smaller amplitude, or it may be missing altogether, while the secondary contraction and redilation upon readmission of light are relatively well-preserved. This is because the retinal 'off' is much weaker than the retinal 'on' wave. In the case of low intensity adapting light, no effective 'off' signal would be generated, whereas, in the case of a very short dark period, the pupillary dilation elicited by the 'off' discharge would be overpowered by the contraction evoked by the more intense 'on' discharge that follows it before the pupil has had a chance to dilate (Loewenfeld, 1999; Lowenstein & Loewenfeld).

The pupils of a healthy, well-rested subject in darkness usually are quite stable for minutes. They remain large and steady as long as the subject stays fully alert, but, under the influence of boredom, fatigue takes over and the pupils begin to oscillate. These oscillations are called 'fatigue waves'. They differ in timing and extent from 'pupillary unrest' fluctuations. They are rather slow (3 sec or longer) and vary in depth from a just perceptible wavering to huge ups and downs, while light-induced 'pupillary unrest' consists of small wavelets that increase in frequency with the intensity of illumination.

C) Psychosensory (reflex) dilation

In response to sensory or central nervous stimulation of an intact, conscious subject, the subject's pupils dilate rapidly and may reach maximal size. Any sensory stimulus, except for light stimulus, and also spontaneous thoughts or emotions have the same effect and serve as a non-specific afferent path for pupillary reflex dilation. After the repetitive administration of the same stimulus this response quickly disappears (habituation).

With regard to the known neurophysiology of pupillary dilation, it does not seem likely that this response is under subcortical initiation and control. Psychosensory dilation is obtained only when cortical influences (either direct to the hypothalamus or mediated through thalamic pathways) remain intact. Impulses from the cortex through cortico-limbic connections (cortico-thalamo-hypothalamic pathway) arrive at the hypothalamus and bring it into play as the major motor centre for the active sympathetic component of the pupillary reflex dilation. From the hypothalamus efferent discharges travel along the sympathetic pathway to the iris dilator muscle of the eye. Under the influence of more intense or longer stimuli there is a biphasic or even a triphasic response (Loewenfeld, 1999).

Neurotransmitter Receptors of the Iris

The two main controlling systems of the iris are thought to be its sympathetic and parasympathetic innervations. Increased parasympathetic activity results in miosis due to the release of acetylcholine at the neuroeffector sites on the iris sphincter muscle and increased sympathetic activity results in mydriasis, which is due to the release of noradrenaline to the neuroeffector sites on the dilator muscle.

The iris sphincter muscle contains cholinoreceptors of the muscarinic type, muscarinic receptors $M_{1, 2, 3}$ (Sitaram et al., 1983; Hutchings & Holly Field, 1984). $M_{1, 3}$ subtypes are located at post-junctional sites, inducing the contraction of the sphincter muscle, whereas M_2 muscarinic receptors are probably located pre-junctionally (Bognar et al., 1989, 1990). The muscle also contains a small number of a- , b- adrenoreceptors, which probably serve for the relaxation of the sphincter during noradrenaline release

from the noradrenergic terminals of the dilator muscles (Sitaram et al., 1983; Jaanus et al., 1989; Morad et al., 2000).

The iris dilator muscle contains mainly a- and very few b- adrenoreceptors (Wilhelm et al., 2001) and the basic subtype for mydriasis is the a_1- adrenoreceptor (Sitaram et al., 1983; McLaren et al., 2002). There is also a parasympathetic inhibitory innervation of the dilator muscle, which is probably partially mediated via M_2 muscarinic receptors located pre-junctionally on the iris noradrenergic nerves to mediate inhibition of noradrenaline release and thus relaxation of the dilator muscle during miosis (Fuder et al., 1986; Bognar et al., 1989).

Moreover, there are also other transmitters considered to mediate pupillary responses to light. Serotonin (5-hydroxytryptamine, 5-HT) is considered as a putative modulator of the neurotransmission of the iris (Szabadi & Bradshaw, 1996). Specifically, 5-HT_2 receptors may play a role in the control of pupillary responses, either via direct postsynaptic 5-HT_2 receptor mediated dilation or via pre-synaptic inhibitory 5-HT_2 receptors modulating parasympathetic tone (Millson et al., 1991). Morphine and opioids are also thought to have a peripheral or central action in the iris (Klemfuss & Adler, 1986). Furthermore, some peptides like tachykinins, substance P and neurotensin are believed to induce miosis (Alessandri et al., 1991).

II. Outline and objectives of the present project

INTRODUCTION

Excessive Daytime Sleepiness (EDS) and Obstructive Sleep Apnea (OSA)

Estimates suggest that up to 1 in 8 adults' experiences excessive daytime sleepiness that is severe enough to interfere with daytime activities (D'Alessandro et al., 1995). This problem can affect alertness, work, education and relationships and lead to accidents (Aldrich, 1989). The causes of EDS can be simply due to insufficient night-time sleep (e.g. due to lifestyle). Other causes include circadian rhythm disturbances (e.g. related to shift work) or medical problems that disturb sleep (e.g. pain, disrupted breathing, restless leg syndrome). EDS can be a feature of depression (Billiard et al., 1994), anxiety or degenerative conditions such as Alzheimer's or Parkinson's disease or even a side effect of the treatments used for these conditions (e.g. dopamine agonists) (Homann et al., 2002). Other potential causes of EDS include alcohol or benzos, sedating antihistamines and drugs that can interfere with night-time sleep such as nicotine-replacement therapy or caffeine. Sometimes EDS is due to narcolepsy. The most common underlying cause of EDS in patients referred to a sleep specialist is Obstructive Sleep Apnea (OSA) (Punjabi et al., 2000).

In people with OSA, as sleep begins and muscle tone relaxes, the upper airway collapses. This causes either total obstruction of the lumen and no respiratory flow (apnea) or partial obstruction leading to shallow breathing (hypopnea), thence the widely used apnea/hyponea syndrome, which is also used to describe this condition. This then triggers transient arousal from deep sleep to a lighter sleep or wakefulness. The person then falls more deeply asleep again and the whole cycle repeats itself, perhaps many hundreds of time a night. The repeated arousals shorten night-time sleep and result in EDS (Engleman et al., 1994; Dement et al., 1994). Other characteristic features of OSA include snoring and choking episodes during sleep, and unrefreshing sleep. OSA is more likely with increasing age and it is estimated that up to 4% of middle-age men and up to

2% of middle-aged women have the condition (Young et al., 1993). People who have it are often obese, particularly around the neck and the condition is also more likely in those who smoke, use sedative drugs or drink alcohol. Besides obesity, there is also high commorbidity with hypertension, obstructive pulmonary disease and metabolic disorders especially diabetes mellitus (Kales et al., 1985; Hung et al., 1990; Partinen & Guilleminault, 1990; Lavie et al, 1995).

Measuring EDS and OSA

Assessment of the severity of the condition is performed by assessing the severity of the EDS and the severity of the OSA. In the assessment of the severity of OSA the nPSG is the indicated test, which provides a number of indices such as the apnea/hypopnea index (A/H), arousal index (AI), mean O_2 saturation and many others. Clinical assessment also includes interviewing the patient's bed partner where possible, measuring the patient's weight, height and BMI, neck, hip and waist circumference. In the assessment of EDS the Epworth-Sleepiness Scale (ESS) (see appendix) and the MSLT are the international gold standards assessing subjective and objective data respectively (Johns, 1991). A total score of above 10 (out of 24) on the ESS suggests abnormal sleepiness. Patients with moderate to severe OSA generally have scores above 16 (Johns, 1991).

Measure of physiologic or pathologic daily sleepiness is a significant problem for every sleep clinic or laboratory. Until today, MSLT is considered to be the 'gold standard' for the objective assessment of sleepiness. However, the test is very expensive, laborious (lasts about 23 hours), quite intrusive, not easily repeated and requires highly trained stuff. Moreover, 'micronaps' (transient periods of reduced alertness just before the beginning of sleep) are not estimated in this test. Also, in many disorders, such as OSA, the MSLT is not correlated with subjective scales of sleepiness. The ideal test for the assessment of somnolence should be based on physiology and should be cheap, fast, easy to use, not intrusive and easily repeated. The pupillary sleepiness test (PST) is a new method that comprises most of these characteristics.

The premises of the Pupillary Sleepiness Test (PST)

The pupils of healthy well-rested subjects in darkness are usually quite stable for several minutes at a time and the normal "pupillary unrest" that occurs under diffused light ceases promptly as soon as the light is turned off. The pupils then remain large and steady as long as the subject stays fully alert, but when the subject remain quietly in darkness for lengthy periods without anything to do, its pupils begin to oscillate and also to decrease in size. This phenomenon was attributed to the influence of boredom and/or fatigue and these oscillations were called “fatigue waves” (Lowenstein et al., 1963). Pupil size in darkness is controlled by the sympathetic system in two ways. First, noradrenergic neurons of the brain stem innervate sympathetic spinal column nuclei and exert an excitatory influence on the peripheral sympathetic, including the iris dilator muscle. Second, an important central role is played by dual inhibitory tone on the parasympathetic neurons of the pupillomotor Edinger-Westphal (EW) nucleus directly from the nucleus locus coeruleus and indirectly from A1/A5 noradrenergic nuclei via the hypothalamus (Szabadi & Bradshaw, 1996). Thus, changes in pupil size in darkness are believed to be the result of variable inhibition of the EW nucleus as a result of fluctuations in central sympathetic activity (Loewenfeld, 1963). After the first description of ‘fatigue waves’ (Yoss et al., 1969), Yoss et al., (1970) first attempted to use these pupillary signs to measure sleepiness in patient groups with chronic sleep disorders, such as narcolepsy and sleep apnea syndrome, and attempted the staging of sleepiness on pupillometric criteria. Despite promising results, research was hampered by serious technical problems until the developments of video techniques and image processing during the 1970s and 80s. However, it was not until the early 90s - when serious methodological problems were addressed - that the study of pupillary size and oscillations in relation to sleepiness was given a real impetus.

Sleep research with the Pupillary Sleepiness Test

The PST as applied today offers an easy, practicable and time-saving (about 11 min) method to record sleepiness-related reduction in pupil size and pupillary oscillations and evaluate them mathematically. It builds upon basic understanding of the mechanisms

mentioned above. Details of the method of recording and data management are described in detail by Lüdtke (Lüdtke et al., 1998). The PST demonstrates circadian changes in alertness and an exponential increase in sleep-deprived healthy normals (Wilhelm et al., 1998b, 2001), correlating well with sleep latency from the MSLT. PST indices present with an exponential increase in healthy sleep-deprived individuals (Wilhelm et al., 1998b; Morad et al., 2000) and subjective rating of sleepiness correlates significantly with instability of pupil size (Pupillary unrest index, PUI) in healthy subjects (Wilhelm et al., 1998b). Patients with chronic sleep disorders, including OSA, differ significantly from normals in terms of PST indices (Lichstein & Johnson, 1993; Wilhelm et al., 1998a; O' Neil et al., 1996) and show clear improvement by a decrease of sleepiness waves after treatment. Additionally, in patients with sleep apnea subjective impairment in daily life correlates significantly with their PST results and patients with more severe breathing disorder at night have significantly higher PST values in the morning than those with fewer apnea events (Wilhelm et al., 1998a). Normal values for healthy adult male subjects have been defined to permit comparison with sleep apnea patients and to calculate specificity and sensitivity of the PST. Nevertheless, PST indices cannot be considered as physiologic sleepiness indices yet, because their results are from a single study of 144 healthy policemen, who referred having normal sleep, denied any sleep disorder and had only one pupillometry recording in the morning (Koerner et al., 1998; Wilhelm et al., 1999). The same study showed significant Spearman's rank correlation (r=0.31) between self-assessment with SSS and PST indices. Another study (Keegan & Merritt, 1996) showed significant correlation between fluctuations of the pupil size and EEG indices. Sleep latency, as measured with MSLT (Carskadon et al., 1987), the size (Merritt et al., 1998) and the number of pupil oscillations (Merritt et al., 2000) depend on the time of day of the recording. The most recent study that indicated PST as an objective, physiologic sleepiness test, in a parallel recording and in comparison with MSLT, found significant increase in two theta EEG power ratios for every pupil staging in narcoleptic and apneic patients (Merritt et al., 2004). However, PST lasts at least 10 minutes and for that reason can be hampered by droopy eye lids, blinks, eye movements and corneal drying. Thus, in the present research we study the effects of a modified PST, which lasts less (5 min) and measures only pupil size.

AIM

This is a preliminary study serving as a pilot to a larger project aiming to validate the modified PST against the MSLT and examine the relationship between the modified PST and daytime sleepiness. Besides for testing the feasibility of the modified PST technique, the primary aim of the present pilot study was to test its face and predictive validity. For this reason we set out to explore whether the modified PST outcome measure (resting pupil size) would correlate with subjective measures of sleepiness and with objective indices of severity of sleep apnea (face validity) and whether the technique would be sensitive to the effects of modafinil (predictive validity), an alertness provoking drug used for the treatment of EDS. The prediction was that the more severe the OSA/EDS, the smaller the resting pupil size would be, and that modafinil would increase it.

The resting pupil size is regulated at all times by the relative influences of the sympathetic and parasympathetic inputs to the dilator and constrictor muscles of the iris respectively. A modafinil-induced increase in resting pupil size could be due to either a modafinil-induced increase in central sympathetic or a modafinil-induced reduction in central parasympathetic tone, or both. A secondary aim of this study was to dissect the relative influences of modafinil on the sympathetic vs. the parasympathetic branches of the autonomic nervous system, using the pupillary light reflex as a test system. It is well known that the amplitude of the light reflex response is a purely parasympathetically mediated response, while the 75% recovery time of the light reflex (the redilation of the pupil in response to light stimulus offset) is largely dependent on intact sympathetic function of the hypothalamus and the peripheral sympathetic chain (Loewenfeld, 1999; Smith S.A., 1992).

Modafinil

Modafinil is an effective and well-tolerated drug with an approval (in Greece as well) for the treatment of narcolepsy (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000; Moldofsky et al., 2000; Broughton et al 1997), which is recommended for the treatment of residual EDS in patients who remain sleepy despite nCPAP therapy

(Arnulf et al., 1997; Heitmann et al., 1999; Pack et al., 2001). Lately, modafinil has been used effectively for the treatment of idiopathic hypersomnia (Bastuji & Jouvet, 1988), for the improvement of somnolence and cognitive performance in sleep-deprived 'normal' subjects after prolonged work (Batejat & Lagarde, 1999; Buguet et al., 1995; Caldwell et al., 2000), for fatigue caused by multiple sclerosis (Rammohan et al., 2002; Zifko et al., 2002) and Parkinson's disease (Hogl et al., 2002; Nieves & Lang 2002) and as a reinforcer of antidepressant treatment, especially when the prevalent symptoms of depression are lack of energy and fatigue (Ninan et al., 2001; Bielski et al., 2001). Modafinil differs chemically and has a different pharmacological profile from other CNS stimulants. Its mechanism of action is still unknown, but it seems that modafinil is associated with modification of GABA release in the AH, while by acting on tuberomammillary nucleus of hypothalamus it increases histamine release and activates the histaminergic pathways, which excite CC, producing alertness and improvement in tasks such as problem solving (Scammell et al., 2000). Modafinil has a minor or no effect on dopaminergic system, which may interprets its low potential for abuse (Jasinski & Kovacevic, 2000). It also produces daytime vigilance without causing adverse effects on nighttime sleep (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000; Moldofsky et al., 2000) and has a minimal effect on the function of cardiovascular, respiratory and gastrointestinal system (Moldofsky et al., 2000; Mitler et al., 2000).

Secondary Aims - Actions of Modafinil on aspects of Cognition

- Attention
  - Selective
  - Sustained
  - Reaction time
- Visual memory
  - Recognition
  - Recall
- Executive function
  - Planning and problem solving ability

III. METHODS

Subjects

The study was approved by the Ethics Committee of the University of Crete and all participants gave their written informed consent prior to screening. We restricted our sample to patients with a recent (< 10 days) diagnosis of obstructive sleep apnea with no commorbid conditions, normal laboratory findings, absence of obesity (BMI < 30), age between 30-50 years, unmedicated and not yet under nCPAP treatment, absence of ocular disorders. All the above factors are known to affect OSA and/or EDS (e.g. obesity, Vgontzas et al., 1998) severity or they are known to interfere with our pupillary outcome measures (e.g. age, ocular disorders). After eliminating extraneous sources of variance, we included patients with a full range of disease severity (from mild to severe), in order to obtain the "true" disease-related variance, thus maximising the chances of detecting correlations between outcome measures and disease and EDS severity. Eleven right handed, male patients were recruited from the Sleep Laboratory of the Respiratory Clinic of the University Hospital of Heraklion on the basis of the above criteria and their characteristics are shown in Table 1. Only three patients were non smokers, the rest smoking from 10 to 80 cigarettes per day. All of them were regular caffeine and only social alcohol consumers. Patients were instructed to maintain their normal patterns of caffeine and nicotine consumption the morning of experimental testing.

	Age	Weight	BMI	ESS	A/H index	Arousal index	Severity	Cigarettes/day	Years of Education
#1	42	98	33.85	3	13	29	Mild	30	16
~~#2 (F)~~	~~41~~	~~74~~	~~27.58~~	~~3~~	~~26~~	~~20~~	~~Mild~~	~~0~~	~~16~~
#3	36	83	28.07	2	21	20	Mild	0	9
#4	41	78	26.06	15	19	33	Moderate	0	9
#5	38	90	28.68	5	40	20	Moderate	10	16
#6	46	99	31.60	19	65	58	Severe	80	2
#7	35	93	32.14	6	72	34	Severe	10	9
#8	49	80	27.01	15	63	42	Severe	20	17
#9	40	96	33.96	6	80	60	Severe	20	14
#10	36	86	27.14	6	33	40	Severe	0	19
#11	48	88	27.77	18	79	65	Severe	50	6
#12	31	119	32.28	18	29	22	Severe	25	9
Mean	**40.25**	**90.30**	**29.68**	**9.67**	**45.00**	**36.92**			
SD	**5.46**	**12.06**	**2.87**	**6.69**	**25.04**	**16.43**			

Table 1. Subjects' characteristics.

Design and drugs

Modafinil 200 mg was administered in two weekly sessions, using a placebo controlled double-blind, cross-over design. The procedures were identical in the two experimental sessions. Onset of sessions was always at 11:00 sharp for all patients with a pre-drug testing (30 min – see below) immediately followed by ingestion of the capsule (placebo or modafinil 200 mg). Two hours after capsule ingestion i.e. always at 13:30 sharp, the patients underwent an identical post-drug testing (30 min) at the end of which they were engaged in cognitive testing lasting for about 1 hour. The timing of post-treatment testing starting at 13:30 was deliberate since at this time of day circadian rhythms reach a nadir, thus maximising chances of detecting a modafinil effect on

pupillary, physiological and cognitive outcome measures. Pre- and post- treatment testing of cognitive functions would have prolonged the testing by another hour and would have resulted in an unwelcome within- and even between-session learning effect which could have seriously compromise the detection of any treatment effects on cognition. It was therefore decided that cognitive testing should take place only post treatment, thus allowing only for placebo vs. modafinil comparisons.

Tests, Stimuli and Apparatuses

Pupillometry

A binocular infrared television pupillometer (PROCYON, P2000D) was used to monitor pupil diameter in darkness in previously dark-adapted eyes (for 15 min). The sampling rate of the pupillometer was 25 Hz, the spatial resolution was better than 0.05 mm and the accuracy was better than ±3%. The recordings took place in a dark, sound-attenuated room. First, the light reflex was elicited and recorded in darkness. The stimuli were light flashes of 200 ms duration delivered via a light emitting diode, presented to the subject's right and left eye in an alternating fashion, as a white disk of 8^{o} diameter, providing "full field" light stimulation (at four levels of stimulus luminance: 0.35, 5, 50 and 140 cd m^{-2}), while the non-stimulated eye was fixating a target dot projected at a distance of approximately 10 m. Each one of the four levels of stimulus luminance was presented in ascending order, in a block of 4 stimuli the average of which was the response for that luminance level. The interstimulus interval within blocks was fixed at 5 s. Therefore, the total time for the elicitation and recording of the light reflex was 80 s. Stimulus presentation was computer controlled, and pupillary measures were digitized and stored for off-line analysis. The parameters studied were: light reflex response amplitude [i.e. the difference between the baseline (defined as the mean pupil diameter recorded over 500 ms prior to the onset of the light stimulus) and the diameter reached at the trough of the pupillary response to the light stimulus] and 75% recovery time (i.e. the time taken for the pupil to reach the 75% of its original size from the moment it reached its maximum constriction to a light flash). Following the elicitation and recording of the

light reflex response, a simplified version of the PST was used. Pupil diameter was monitored and recorded intermittently every 10 s, for fifteen consecutive 20 s epochs. The outcome measure was the mean pupil diameter from each one of the 15 epochs. The total monitoring time was 430 s.

Psychological measures

Patients rated their mood and feelings on 16 items 10-cm visual analogue scales (VAS) (Norris, 1971). For each patient, the raw values (cm) for each item were weighted by multiplication with their respective factor loading, and the weighted values for each item were then allocated to "alertness", "anxiety" and "discontentment" factors, based upon a principal component analysis (Bond & Lader, 1974). The average of the weighted values for each factor was entered in the statistical analysis. The VAS were completed in each session, before and two hours after treatment.

Physiological measures

Systolic and diastolic blood pressures (sitting and standing positions) using a manual sphygmomanometer and heart rate were also recorded before and two hours after treatment.

Neuropsychological Testing

With the exception of the Stroop Interference Test (see below), all neuropsychological testing was performed using the Cambridge Neuropsychological Test Automated Battery *(CANTAB*). CANTAB is a set of neuropsychological test batteries developed by Robbins, Sahakian and co-workers and standardized in a large group of normal subjects (Robbins et al., 1994, 1998). The tests in these batteries are non-verbal, administered with the aid of a high-resolution touch-sensitive screen (Advantech), with continuous and sensitive adjustment of levels of difficulty, obviating floor and ceiling effects. Their administration has been extensively described elsewhere (Owen et al., 1990, 1991, 1993).

Attention battery

Stroop Interference Test. The standardized version of this test was used. The administration and scoring procedures are described in detail elsewhere (Bondi et al., 2002). Briefly, here subjects were asked in three consecutive 45-second periods, first to read the names of colours written in black ink, then to name the colour of patterns and finally to identify the colour of ink that is mismatched to a word (e.g. the word *red* printed in blue ink is identified as *blue*). These procedures result in a Word (W), a Colour (C) and a Colour-Word (CW) score. The increase in time taken to identify the colour of the incongruent word list results in fewer correct responses in the 45 sec period and is referred to as Stroop *interference*. Interference scores were calculated as the difference between the C-CW scores. The greater the C-CW difference, the greater the interference effect and the worse the performance in this test. This is a test of selective attention and response inhibition, since the task requires the subject to inhibit the (habitual) response to the semantic value of the word and to (selectively) attend to its colour content. The Stroop test is sensitive to the function of anterior cingulate cortex and DLPFC (Pardo et al., 1990, Peterson et al., 1999).

Rapid Visual Information Processing (RVIP). This is a test that reflects the ability to sustain the function of the allocated processing resources to the task-at-hand, based more on the premises of alertness and vigilance (Sahakian et al., 1989) rather than an inhibitory mechanism and selectional processing. Subjects are asked to detect consecutive target sequences of digits presented at the rate of 100 digits per minute for 4 minutes and responses are registered by a button press. Main performance measures include: total hits (number of targets correctly detected), total misses (number of undetected targets), total false alarms (number of responses made in the absence of targets). From these, calculations of sensitivity (A': tendency to detect target sequences) and response bias (B": tendency to respond regardless of target sequence) are possible, derived from Signal Detection Theory (Sahgal, 1987), which take both hit probability and false alarms into consideration.

Reaction Time (RTI). There are five ascending levels of difficulty in this test, the first four of which act as training exercises to prepare subjects for the final level. At the first stage subjects simply have to touch the screen when a yellow dot appears in the center, neither being too early nor too late. The choice reaction task is introduced at the second stage, with

the dot now appearing in one of five locations. Subjects are introduced to the use of a touch pad at the third level. They are required to lift their hand from the touch pad as quickly as possible after a dot has appeared in a single location on the screen. This requirement to release the pad is combined with the requirement to touch the screen at the fourth level. Subjects are required to hold down the touch pad until a single dot appears in the center of the screen and then to touch position of the dot as quickly as possible. Subjects are now considered to be adequately trained for the fifth and final stage, a five choice reaction time task. They are required to hold down the touch pad until the dot appears at one of five locations on the screen, and then point to the position on the screen where the dot was presented.

Executive Function Battery

Stockings of Cambridge (SoC). This is a modified, computerized version of the Tower of London (Owen et al., 1990). Subjects were asked to compare two different arrangements of "balls" in "socks" (one presented on the top half of the screen, the other on the bottom) and rearrange, in the minimum possible number of moves, the balls in the lower half of the screen such that their positions match the target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial Thinking Time (ITT) prior to execution of the first move, Subsequent Thinking Time (STT) for the execution of all subsequent moves, as well as number of moves required by the subjects to rearrange the balls, and problems solved in minimum moves were recorded. Poor performance [e.g. in hypofrontality (Joyce et al., 2002)] in this test is usually revealed for the difficult 4- and 5-move problems. It translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with more mean moves and less perfect solutions. The opposite is true for high performance in this task. This test is sensitive mostly to the function of DLPFC and anterior cingulate cortex (Cazalis et al., 2003; Lazeron et al., 2000; Dagher et al., 1999; Baker et al., 1996).

Spatial Span (SSP). This test taps on the function of the midventrolateral regions of the prefrontal cortex (Owen et al., 1996). A pattern of white squares is shown on the touch screen. Some of the squares change color, one-by-one, in a variable sequence. At the end

of the presentation, a tone indicates that the participant should touch each of the squares that changed color in the same sequence as they were presented. The task becomes progressively more difficult, as the number of squares in the sequence is increased from two, at the start of the test, to a maximum of nine. There are three sequences at each level of difficulty. If the participant is unable to repeat all sequences at any one level, the three sequences at the next level are presented, but then the test is terminated. Participants are given one practice trial before commencing at the two-square level (Morgan, 1998; Mehta et al., 1999).

Visual Memory battery

Delayed Matching To Sample (DMTS). This test is sensitive to temporal and parietal lobe function (Smith et al., 1995). Subjects are shown a complex visual pattern (the sample) and have to decide which of the four patterns that appear below is identical. On simultaneous trials, the sample remains on the screen while the subject makes his choice. On delay trials, the sample disappears and the choices appear with a delay of 0, 4 or 12 seconds, 40 trials are given, ten simultaneous and ten at each delay (Durlach, 1998). In each case, one pattern is identical to the target stimulus, one is identical in shapes but not in colours, one identical in colours but not shapes and one different in both components (a distracter) (Purcell et al., 1998).

Pattern Recognition Memory (PRM). This test is presented in two phases. In the presentation phase participants are shown a series of 12 simple, abstract, coloured patterns, which appear one at a time inside a white box located in the center of the screen. Each of the "target" patterns appears for 3 s, the screen is cleared and the next pattern appears. In the recognition phase, 12 pairs of coloured patterns appear on the screen (one pair at a time) and the participant is required to respond to each pair by touching the pattern seen during the presentation phase. Each of the target patterns is paired with a distractor pattern that differs from it in form but not in colour. Each response is accompanied by an auditory tone, and visual feedback is provided in the form of a tick, for correct response and a cross for an incorrect response. This procedure is repeated with 12 new patterns and the participants' total score (maximum = 24) is automatically recorded (Rabbitt & Lowe, 2000).

Statistical analysis

Pre-post treatment changes in pupil diameter were derived for each one of the fifteen 20 s epochs. These changes were subjected to a 2 x 15 (treatment x epochs) two-way ANOVA with repeated measures. Furthermore, for each one of the eleven patients, the mean post- treatment pupil diameter was calculated for the placebo and the modafinil treatment by averaging the pupil diameter values obtained in each one of the respective fifteen 20 s epochs. The difference between these two means was defined as the mean modafinil effect on pupil diameter. Following these procedures, Pearson correlation coefficients were used to examine the relationship between indices of disease severity and the mean post-placebo pupil diameter as well as the mean modafinil effect on pupil diameter, obtained in the group of eleven patients. Separate two-way ANOVAs were used to analyse the light reflex amplitude and recovery time with treatment (placebo, modafinil) and light intensity (four levels) as the within-subject factors.

Pre-post treatment changes were derived for VAS data, systolic and diastolic blood pressure and heart rate. These changes were subjected to separate one factor (treatment, two levels) repeated measures ANOVAs.

All neuropsychological performance indices derived from CANTAB, were analysed using separate two-way ANOVAs with repeated measures with the order of modafinil administration (first or second session) as the between- and treatment (placebo, modafinil) as the within-subject factor. Whenever the level of task difficulty was a relevant variable, a three-way ANOVA was used with level of difficulty as a second within-subject factor.

IV. RESULTS

Effects of treatment on resting pupil diameter

Figure 3 (top) shows the pre- and post-treatment values of RPD for each one of the 15 epochs for the placebo and the modafinil treatment, as well as the mean RPD for the placebo and modafinil treatments and their difference (inset). Fig 3 (bottom) shows the Δ pupil diameter for the two treatments. It can be seen that modafinil treatment significantly increased pupil diameter in darkness, compared to placebo in our group of OSA patients. ANOVA confirmed this impression with a treatment main effect [$F(1, 11) = 22.44$, $p < 0.001$]. The epoch main effect and the treatment by epoch interaction were not significant [$F < 1$ and $F(14,154) = 1.58$, $p = 0.09$ respectively].

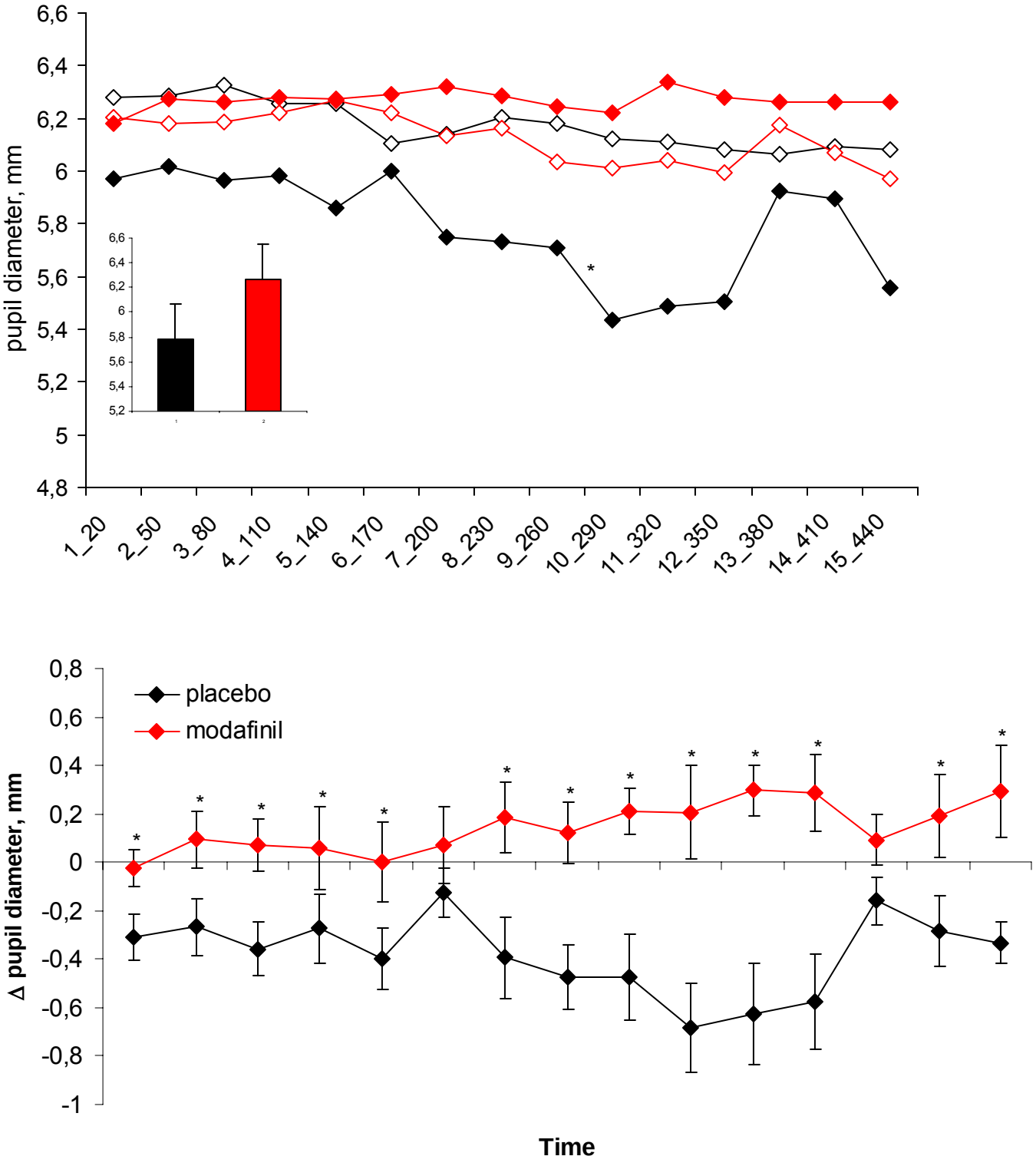


Figure 3. Top panel: Pre- and Post-treatment values of RPD for the placebo and the modafinil treatments. Mean RPD for the two treatments and their difference (inset). Bottom Panel: Δ pupil diameter for the two treatments.

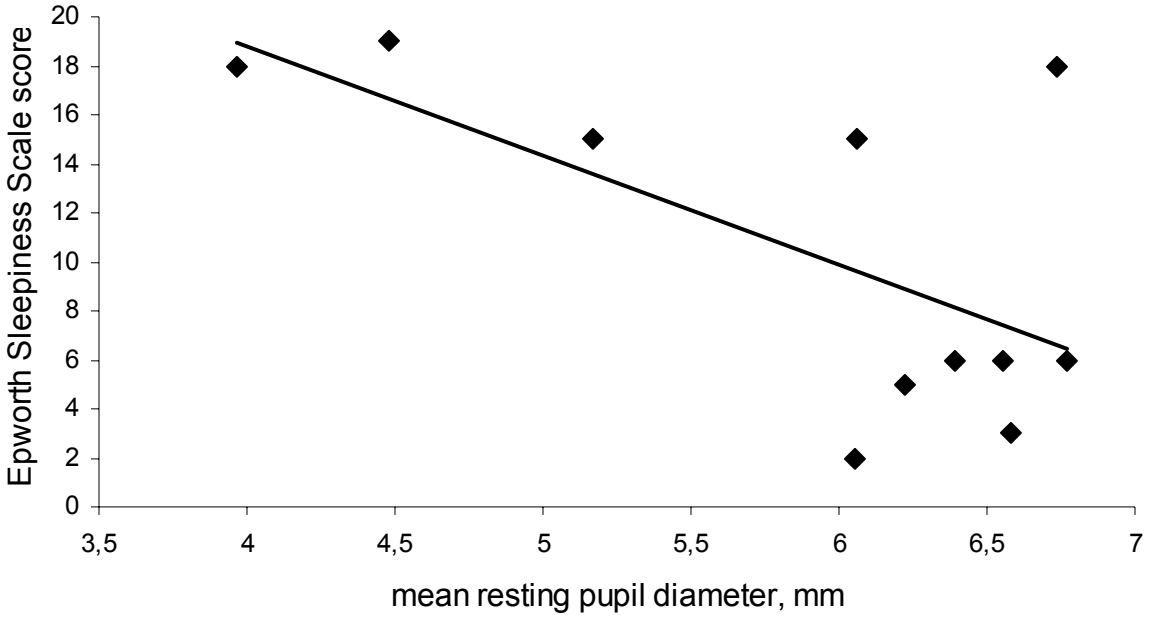
Relationship of pupillary to indices of disease severity

The correlations between the mean post-placebo RPD and the pure modafinil effect on RPD (mean post-modafinil RPD – mean post-placebo RPD) are shown in Table 2. It can be seen that RPD correlated negatively with ESS, AI (see also Figure 4) and positively with the lowest O_2 saturation suggesting that the more the subjective sleepiness experienced at daytime, the greater the arousal time during sleep and the lower the O_2 saturation, the smaller the pupils of the patients when they receive placebo treatment. When the effect of BMI and indices of body fat were partialled out, the relationship of RPD and ESS scores was lost while the relationship of RPD with most of the objective indices of disease severity improved. This suggests that the amount of body fat may be an important and independent determinant of subjective daytime sleepiness regardless of the presence of sleep apnea or its severity.

	ESS	**A/H index**	**Arousal Index**	**TST**	**NRem**	**Rem**	**Mean Sat O_2**	**Lowest Sat O_2**
Mean PD (post-placebo) df:11	-0.63*	-0.49	-0.67*	-0.47	-0.46	-0.43	0.58†	0.70*
Δ PD (mod-plac) df:11	0.77**	0.20	0.13	0.60*	0.57†	0.52	-0.63*	-0.60*
	Controlled for BMI, neck, waist & hip circumference (cm)							
Mean PD (post-placebo) df:5	-0.38	-0.76*	-0.82*	-0.73†	-0.73†	-0.28	0.79*	0.87*
Δ PD (mod-plac) df:5	0.90**	0.31	0.23	0.70†	0.66	0.59	-0.70†	-0.67

* $P < 0.05$, ** $p < 0.01$, † $p < 0.08$

Table 2. Correlations between the mean post-placebo RPD and the pure modafinil effect on RPD (mean post-modafinil RPD – mean post-placebo RPD).



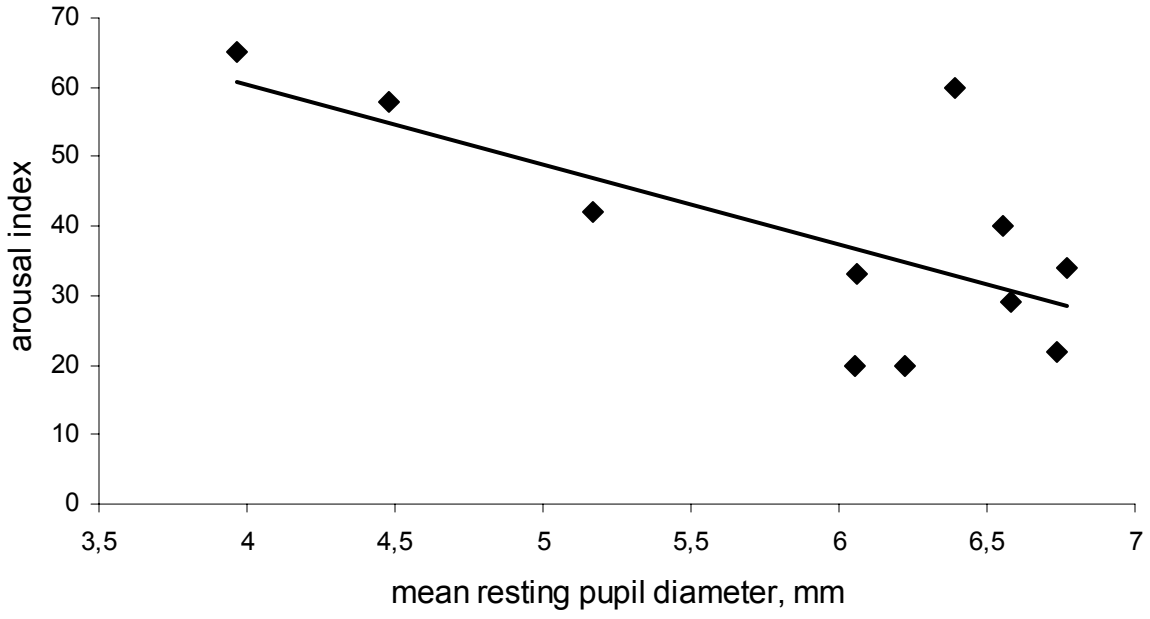


Figure 4. Correlations between RPD and ESS and AI.

It can also be seen in Table 2 that the effect of modafinil on RPD correlated positively with ESS (see also Figure 5) and negatively with mean and lowest O_2 saturation suggesting that modafinil exerted its greatest effects on RPDs of the most severely affected patients. It can be seen that in contrast to post-placebo RPD partialling out the effects of body fat the relationship between the effect of modafinil and ESS scores was not lost and in fact it was improved. This suggests that the modafinil-induced increase on RPD is independent of the influence of body fat on patients' subjective sleepiness reports.

Although objective nPSG indices of OSA severity intercorrelated highly (data not shown), only the lowest O_2 saturation showed a significant negative correlation with ESS scores ($r = -0.66$; $p < 0.05$).

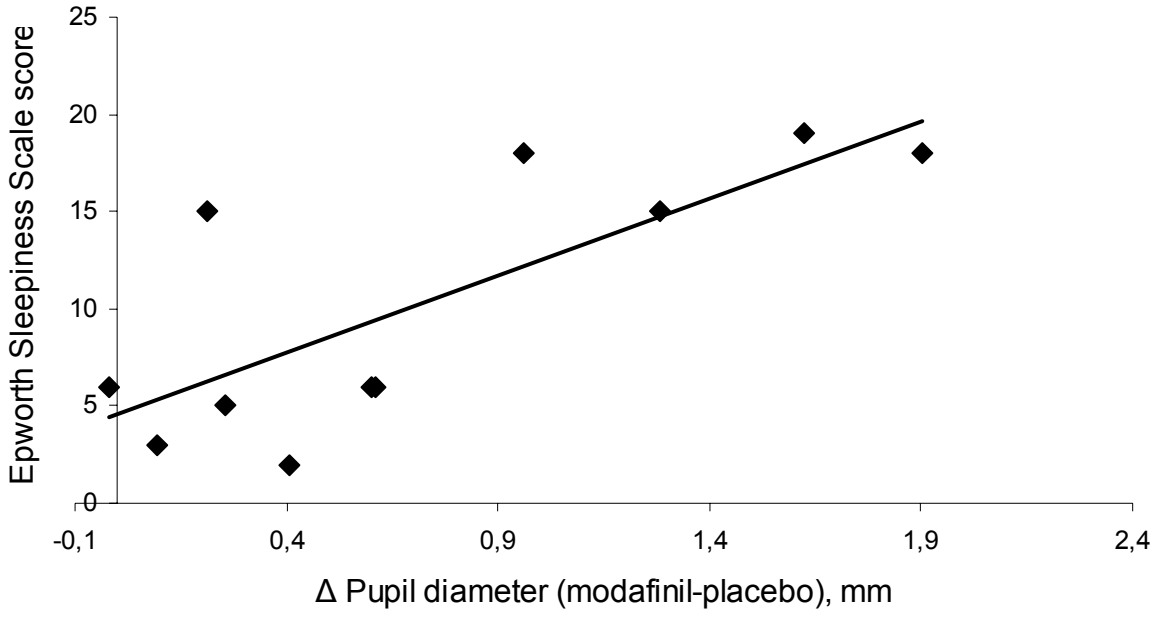


Figure 5. Correlation between Δ pupil diameter in the two treatments and ESS.

Effects of treatment on light reflex

Figure 6 shows the light reflex after placebo and modafinil of a representative patient. It can be seen that modafinil reduced light reflex amplitude while it did not affect 75% recovery time. Figure 7 shows the collective data for light reflex amplitude (top) and 75% recovery time (bottom) for the entire patient group. Light reflex amplitude was increased with increasing light intensity as expected, but it was reduced by modafinil at all light intensities. ANOVA of the amplitude data showed significant main effects of treatment and light intensity [$F(1, 11): 28.58$; $p < 0.001$ and $F(3, 33): 146.23$; $p < 0.001$ respectively) but not a significant interaction ($F < 1$). In contrast to the amplitude data, 75% recovery time was not affected by either light intensity or modafinil treatment (all Fs < 1).

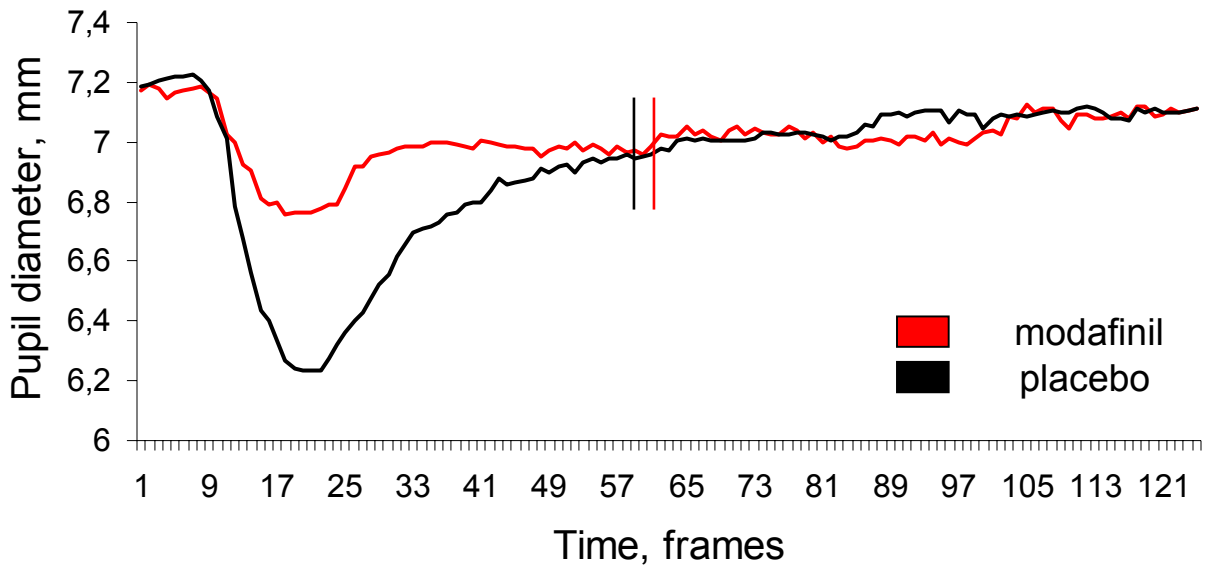


Figure 6. The light reflex after placebo and modafinil of a representative patient.

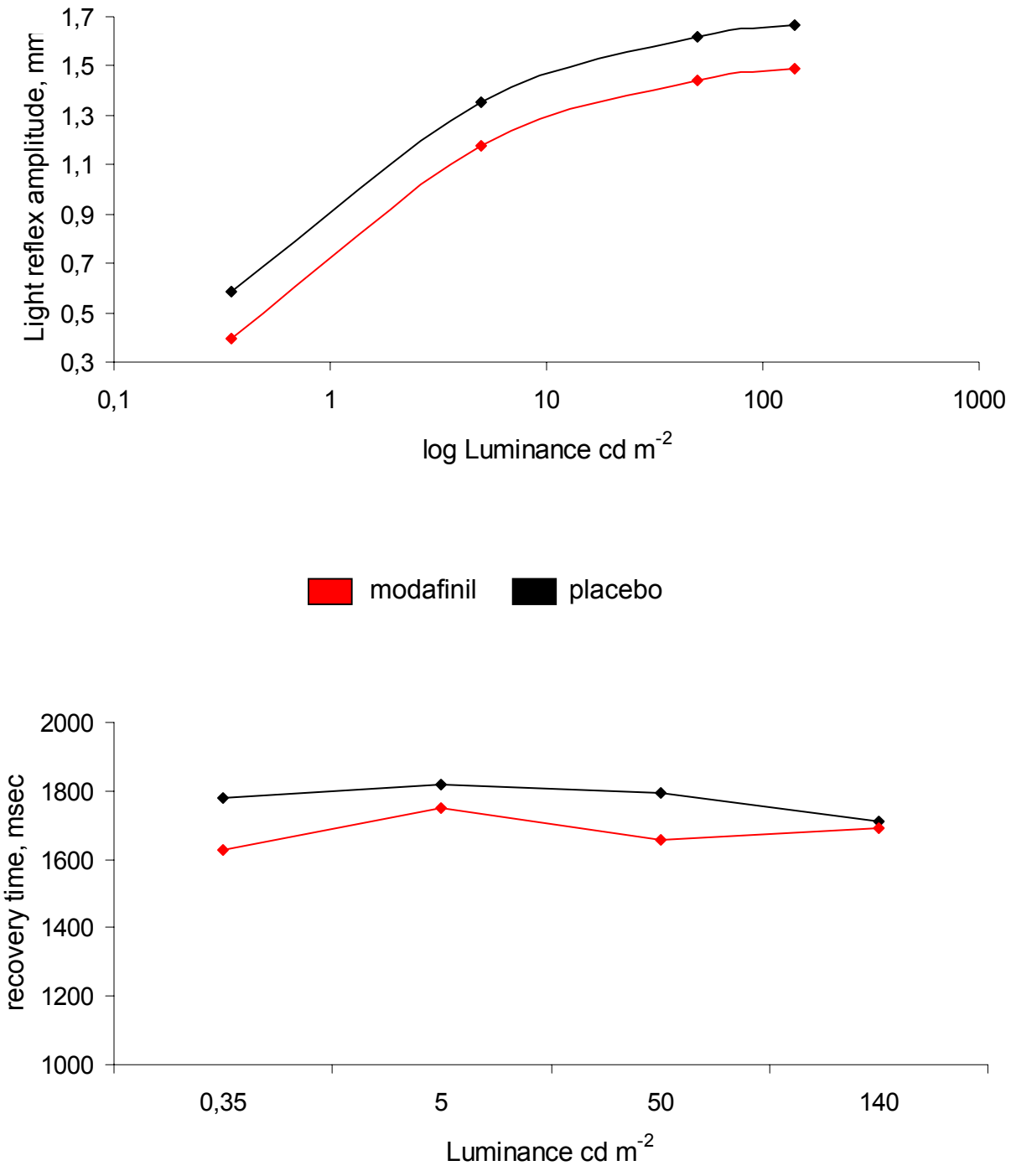


Figure 7. Collective data for light reflex amplitude (top) and 75% recovery time (bottom) for the entire patient group.

Effects of treatment on autonomic and psychological measures

The effects of modafinil on heart rate, blood pressure and VAS measures are shown in Table 3. Modafinil had no effect on the cardiovascular measures and it tended to reduce anxiety and increase alertness, although only the latter was significant at a trend level (see Table 3).

	Placebo	**Modafinil**	**F value**	**P value**
Δ Heart rate	-6.00±1.60	-1.33±1.72	1.80	> 0.1
Δ BP systolic sitting	0.83±3.42	-5.83±3.19	1.74	> 0.1
Δ BP diastolic sitting	-1.67±2.41	-2.50±5.13	< 1	
Δ BP systolic standing	-0.83±3.36	-5.00±3.64	< 1	
Δ BP diastolic standing	0.00±2.54	-3.33±3.45	< 1	
VAS anxiety	2.58±0.40	1.65±0.33	3.31	**=0.09**
VAS discontentment	2.03±0.28	1.56±0.27	2.20	> 0.1
VAS alertness	4.97±0.32	5.57±0.29	4.34	**=0.06**

Table 3. The effects of placebo and modafinil on heart rate, blood pressure and VAS measures.

Effects of treatment on cognitive function

Executive function

SoC. The results of modafinil treatment on ITT, STT and Problems solved correctly with minimal moves are shown in Figure 8. It can be seen that ITT and STT were increased depending on the level of difficulty. Modafinil increased ITT and reduced STT for all problems. It can also be seen that modafinil increased the number of Problems solved correctly. Separate 2-way ANOVAs with level of difficulty and treatment as the within-subject factors showed significant main effects in the case of difficulty level and significant trends in the case of treatment. The difficulty by treatment interaction was not significant.

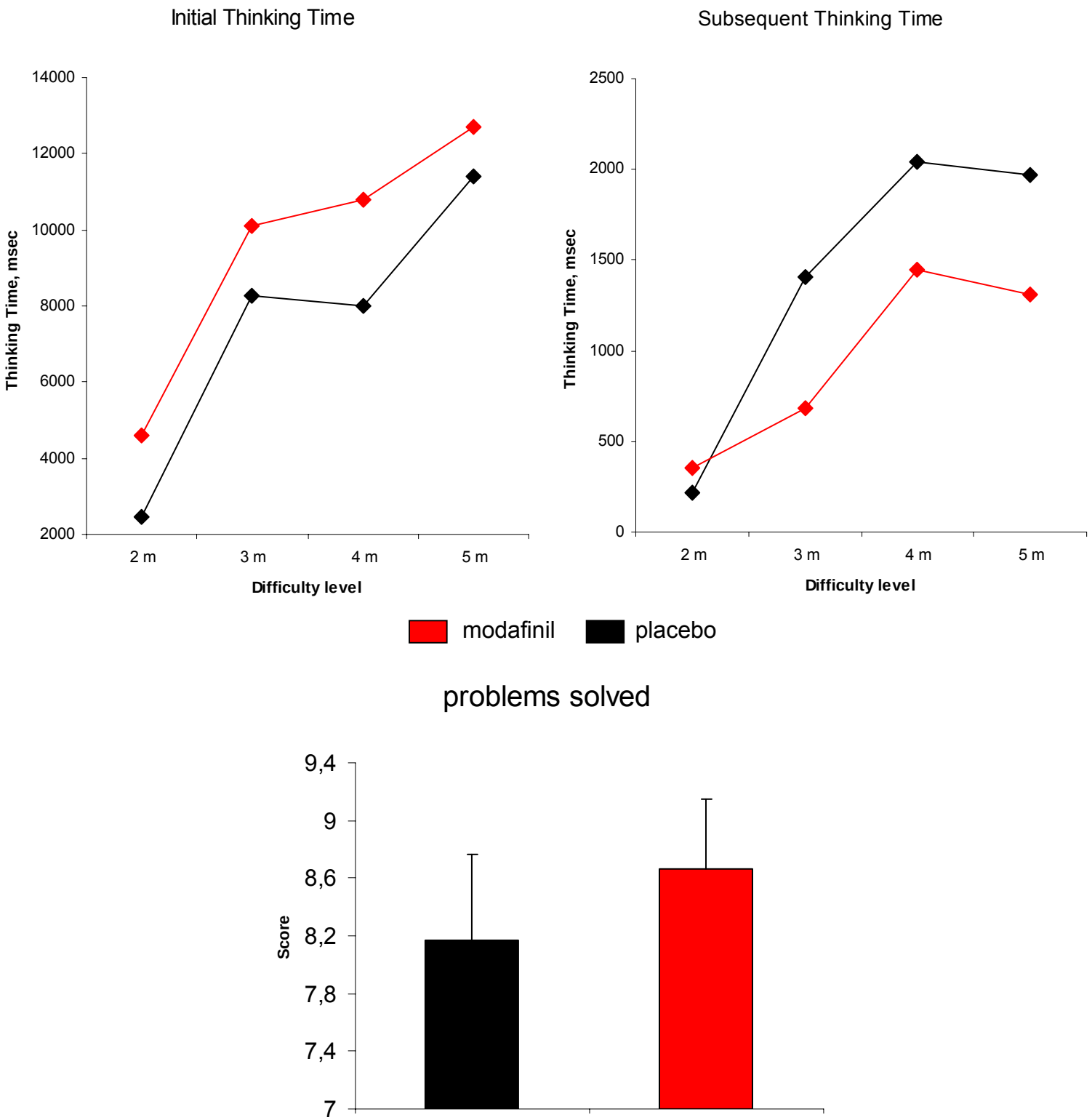


Figure 8. Effects of modafinil on the Stockings of Cambridge test

SSP. The results of modafinil treatment on SSP performance are shown in Figure 9. It can be seen that modafinil increased total usage errors compared to placebo. Two-way repeated measures ANOVA with treatment and order as the within-subject factors revealed a significant treatment main effect [F (1, 9): 5.11; p = 0.05]. The treatment x treatment order interaction was not significant.

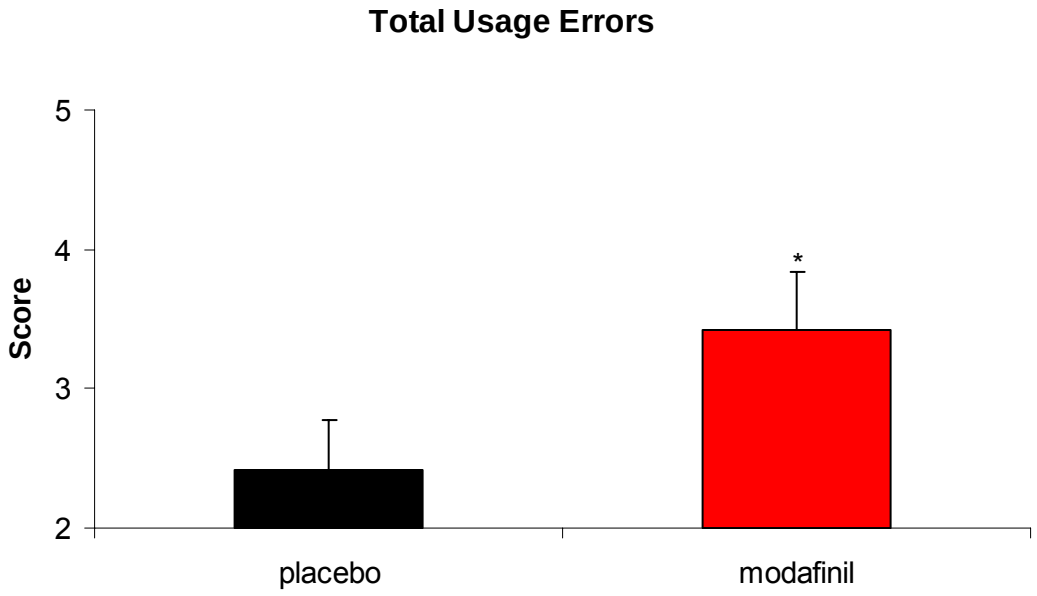


Figure 9. Effects of modafinil on Spatial Span Total Usage Errors

Attention

RTI. The results of modafinil treatment on RTI performance are shown in Figure10. It can be seen that modafinil reduced reaction time compared to placebo. Two-way repeated measures ANOVA with treatment and order as the within-subject factors revealed a significant trend for the treatment main effect [F (1, 9): 3, 87; p = 0.08]. The treatment main effect and the treatment x treatment order interaction were not significant.

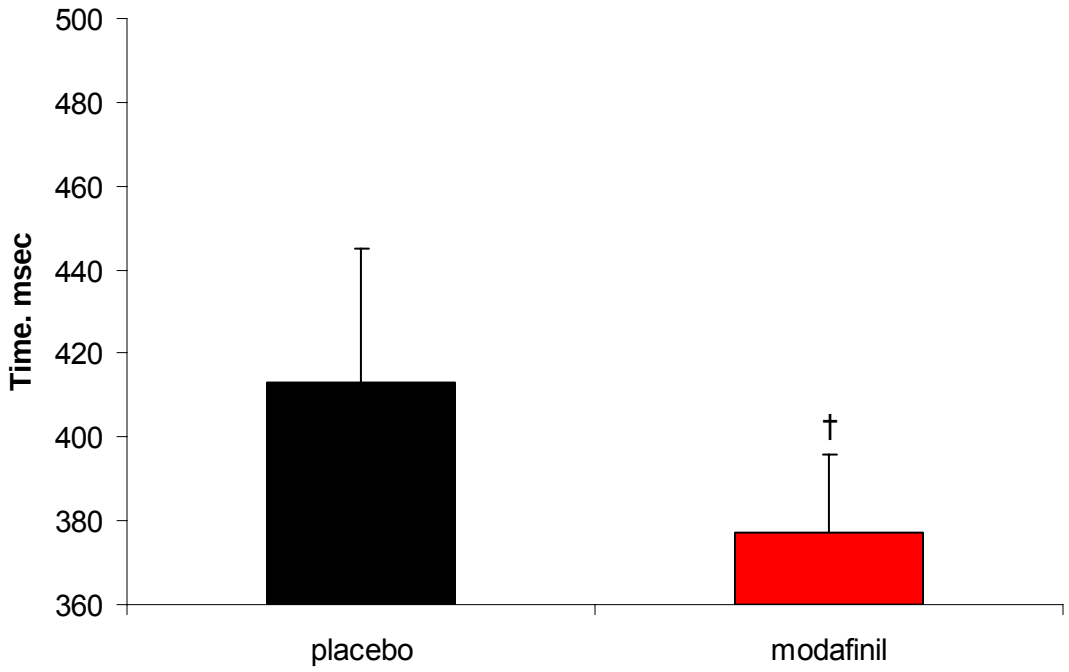


Figure 10. Effects of modafinil on Simple Reaction Time

RVIP. The effects of modafinil on RVIP accuracy (A´ i.e. correct target detection) and latency of responses (i.e. the time required for patients to press the pad after they correctly detected a target sequence) are shown in Figure 11. It can be seen that while modafinil did not increase accuracy of responses [treatment main effect for accuracy measure A´: $F(1, 9): 1.48$; $p>0.1$, see top right panel], it did reduce the time required for patients to press the pad after they correctly detected a target sequence [treatment main effect for latency $F(1, 9): 5.40$; $P<0.05$ see bottom panel].

While the treatment main effect was not significant (see above) the two-way repeated measures ANOVA with treatment and treatment order as the within-subject factors revealed a significant treatment x order of modafinil administration interaction [$F(1, 9): 21.76$; $p<0.001$ (see top left panel)]. This interaction suggests that the group which received modafinil in the second session performed better that the group which received modafinil in the first session. Post hoc comparisons with Bonferoni corrected one-way ANOVAs showed that the better performance of this group was due to their performance in the second session. This suggests that as far as target detection is concerned, modafinil facilitated the effects of learning in the second session.

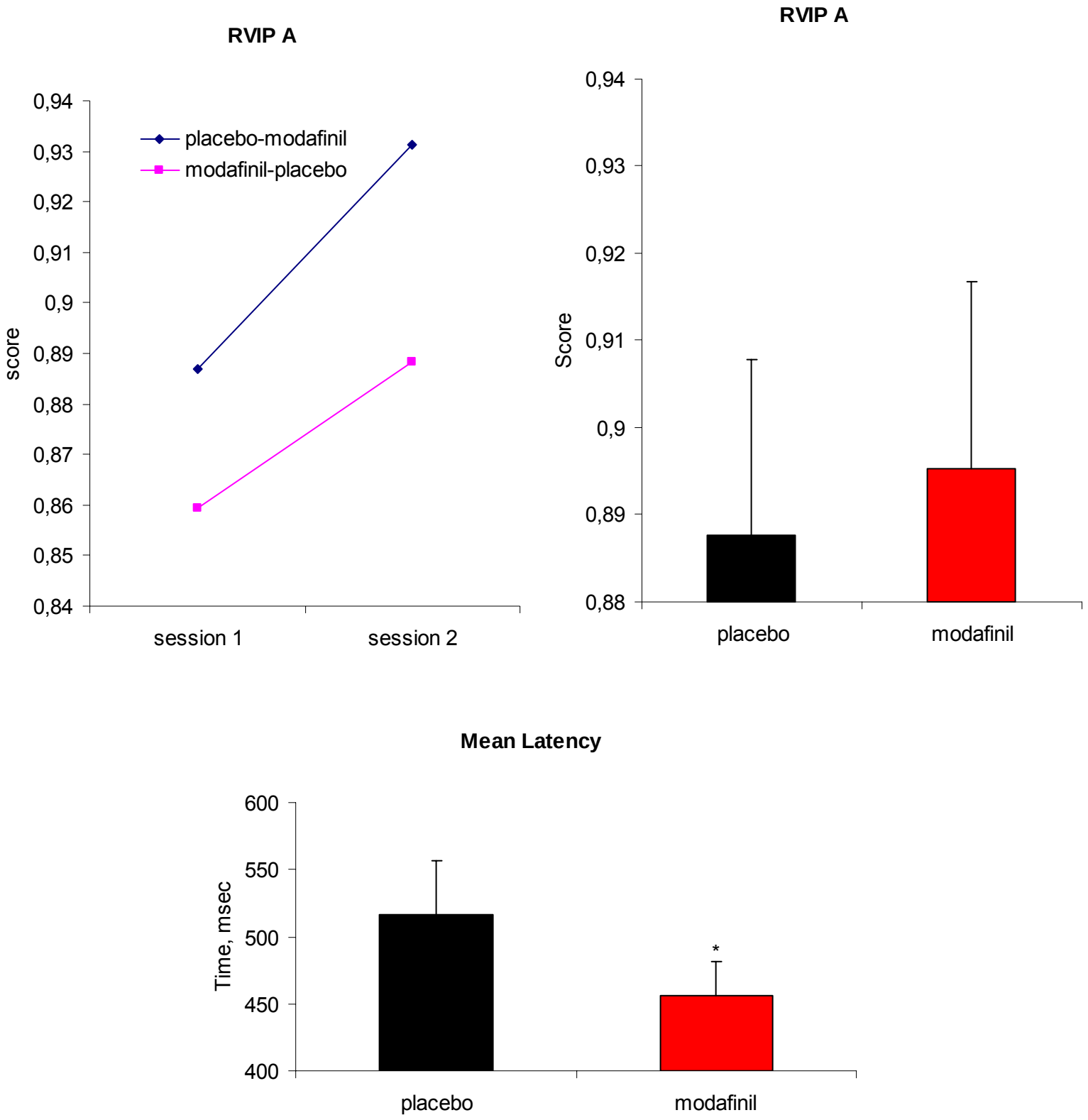


Figure 11. The effects of modafinil on the RVIP test.

STROOP. The effects of modafinil on STOOP performance are shown in Figure 12. It can be seen that modafinil tended to improve STROOP performance but this effect was not significant. Two-way repeated measures ANOVA with treatment and treatment order as the within-subject factors did not reveal significant main effects of treatment or treatment order by treatment interaction.

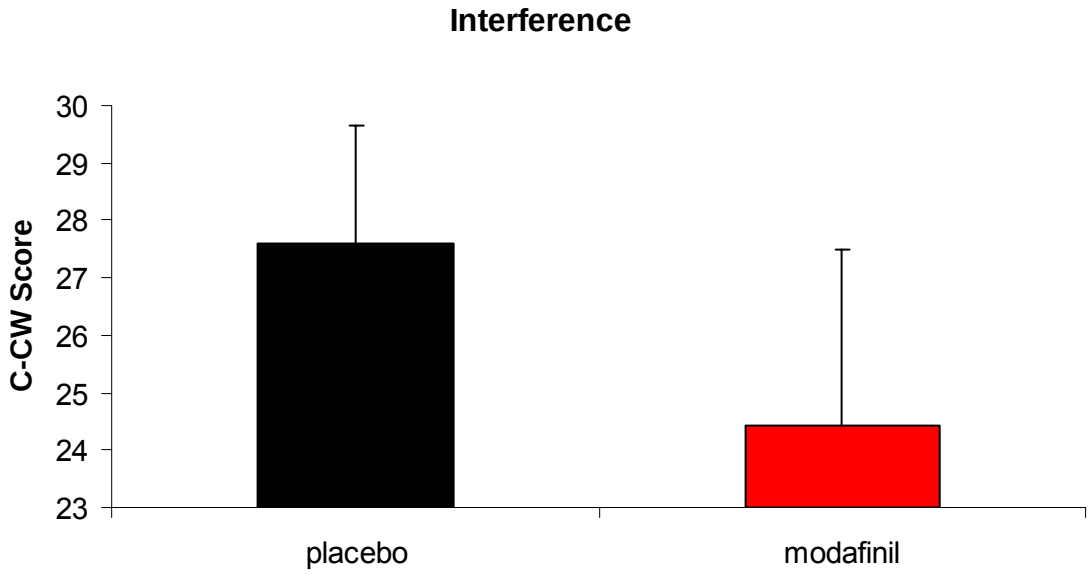


Figure 12. Modafinil had no effect on Stroop test performance.

Memory

PRM. The effects of modafinil on PRM performance indices are shown in Figure 13. It can be seen that modafinil had no significant effects on this task. Separate two-way repeated measures ANOVA with treatment and order as the within-subject factors did not reveal significant main effects of treatment or order by treatment order interaction for any PRM measure.

DMTS. The effects of modafinil on DMTS performance indices are shown in Figure 14. It can be seen that there was a trend for an increase in the time to respond whenever the patients made a correct choice (see bottom left panel) [treatment main effect: $F(1, 9)$: 4.53; $p = 0.06$], suggesting that, as patients became more alert and they spent more time thinking out their responses to the memory task. This is similar to the pattern seen in the planning task when subjects, as they became more alert, spent more time thinking out the solution to the more difficult problems, and as a result had shorter execution times and more problems solved correctly.

There was also a treatment by treatment order interaction for several performance measures in this task (see top panels and bottom right panel). These interactions together suggest that the group which received modafinil in the first session performed better than the group which received placebo in the first session, while both groups performed the same in the second session probably as an effect of learning.

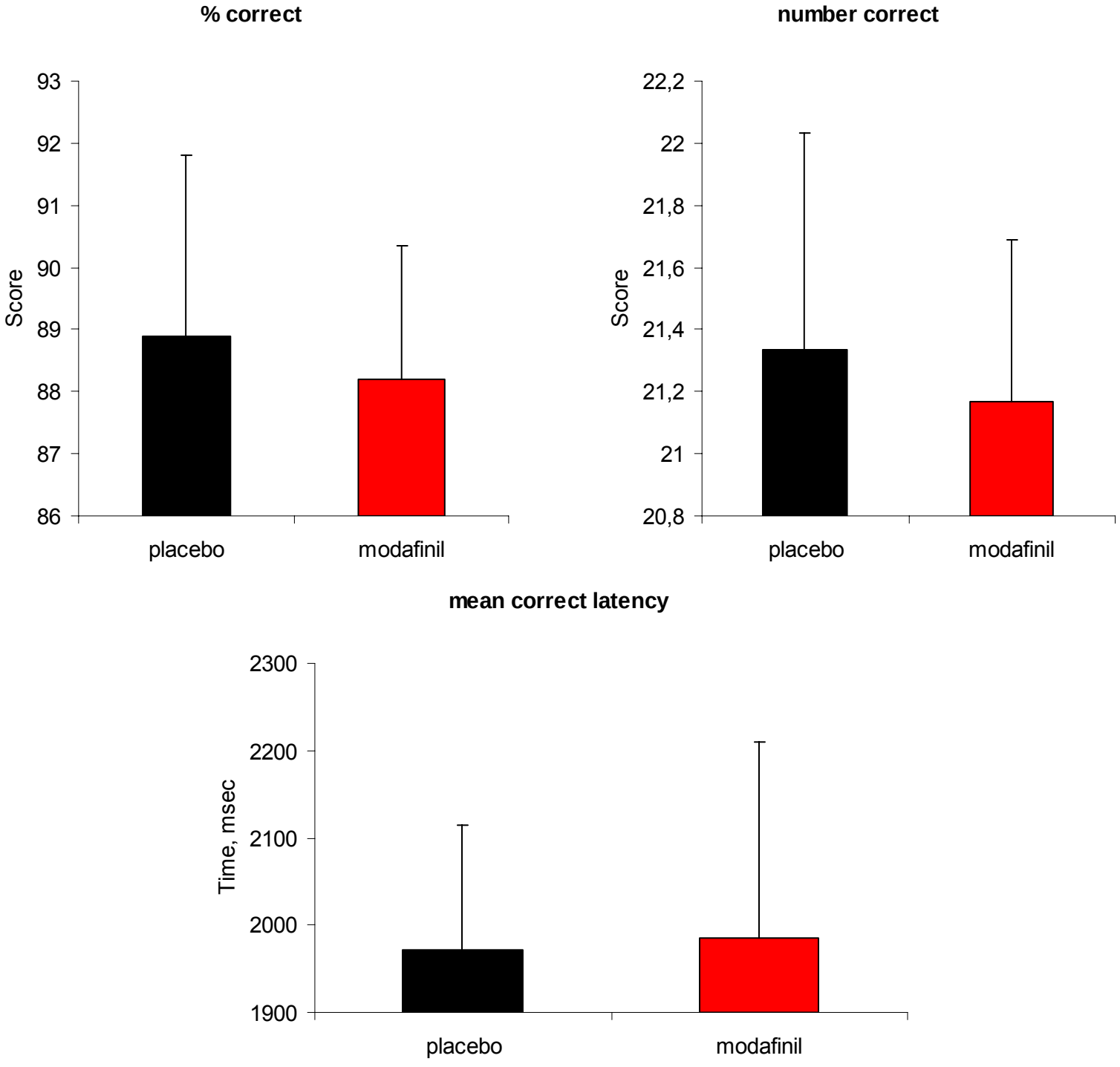


Figure 13. Modafinil had no effects on measures of PRM

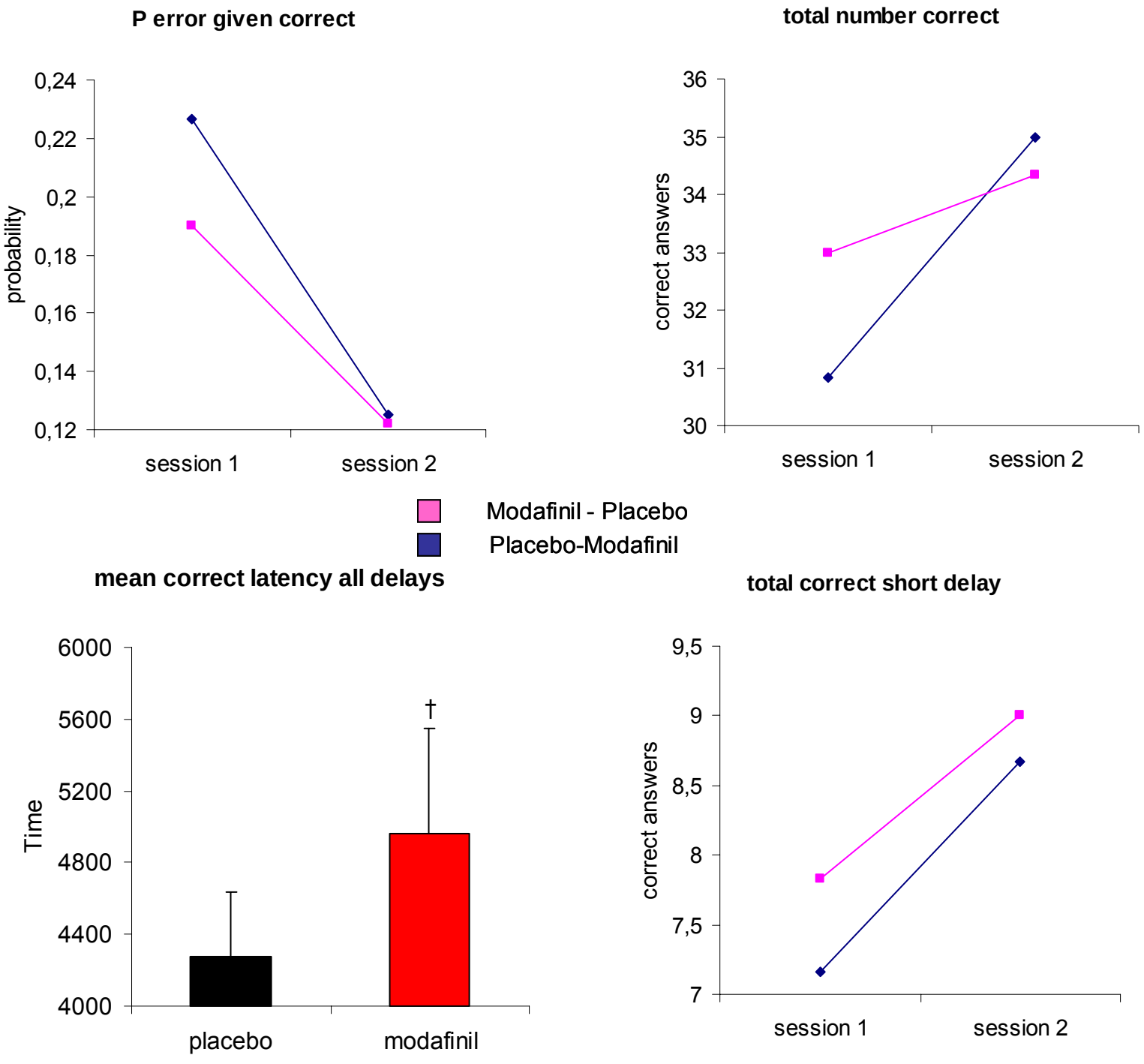


Figure 14. The effects of modafinil on measures of DMTS

DISCUSSION

The present study indicates that pupils of sleep apnea patients have a relatively stable diameter during morning hours (measure at about 11:00 h), whereas they start to decrease in diameter in the afternoon (at about 13:30 h). These results are consistent with former studies, which have shown that time of day is an important factor as concerns alertness. Larger pupils during the day compared to night and also spontaneous low frequency pupillary movements in the morning have indicated that alertness is higher during morning hours (peak point at 09:00 h). Moreover, higher frequency pupillary movements during afternoon hours (followed by a decrease during the evening) and especially during night hours and a daytime peak of sleepiness at 15:00 h in elderlies have indicated that during afternoon and night hours people tend to be sleepier compared to other times of day (Wilhelm et al., 2001; Richardson et al., 1982). Thus, pupil diameter could be proved to be a significant factor for measuring sleepiness.

Instead of the difference in pupil diameter between morning and afternoon hours, our research has shown that pupils of sleep apnea patients have almost the same diameter (with a trend for increase) in the afternoon after treatment with modafinil and in the morning without any treatment. Another important outcome indicates that the mean pupil diameter of sleep apnea patients at about 13:30 h is much bigger after modafinil than in the absence of treatment. Thus, treatment with modafinil seems to significantly decrease excessive daytime sleepiness and improve alertness in a group of sleep apnea patients, a result that has been shown in many other studies with apneic (Arnulf et al., 1997; Kingshott et al., 2001; Pack et al., 2001; Schwartz et al., 2003) and narcoleptic patients (Laffont et al., 1994; Besset et al., 1996; Broughton et al., 1997; US Modafinil in narcolepsy Multicenter Study Group, 1998, 2000; Mitler et al., 2000; Moldofsky et al., 2000). These findings may indicate the predictive validity of the modified PST, which seems to be sensitive to the effects of the vigilance-enhancing drug modafinil.

Pupil diameter after placebo was negatively correlated with ESS and AI scores and positively correlated with the lowest O_2 saturation score, showing that the greater the subjective sleepiness and the arousal index during night time and the smaller the lowest O_2 saturation, the smaller will be the pupil diameter. After partialling out the effect of

BMI and other body mass indices (partial correlations), the negative correlation between pupil diameter and subjective somnolence was lost, whereas the relationship with most of the objective indices of severity of sleep apnea was improved. These results suggest that body mass index alone could be an important factor for subjective sleepiness, regardless of the presence or the severity of sleep apnea (Vgontzas et al., 1998). This is an outcome that proves the sensitivity of modified PST, as patients in our study were not thought to be fat.

The 'pure' modafinil effect on pupil diameter – compared to placebo – was positively correlated with subjective sleepiness and negatively correlated with mean and lowest O_2 saturation. This means that modafinil induced its greatest increase in pupil diameter on the sleepiest and more severe apneics of our patients. After partialling out the body fat indices, the relationship of modafinil's pure effect with subjective sleepiness was improved, while correlations with objective indices of disease severity were reduced or lost. All the above results suggest that the more severe the subjective sleepiness and sleep apnea, the greater the effects of modafinil on pupil diameter. It also seems that the greater the subjective somnolence – no matter what causes it (for instance, body fat or sleep apnea or both), the greater also the effect of modafinil on pupil diameter. These results prove the sensitivity of the new pupillary technique for the assessment of sleepiness as well.

While the objective polysomnographical indices where significantly correlated with each other, they did not show any correlation with subjective sleepiness, except for oxygen saturation. These findings not only demonstrate the sensitivity of the technique but also suggest that it shows better face validity compared to the polysomnographical indices, as concerns somnolence and its severity.

Pupil diameter is a dynamic equilibrium in the opposite effects of sympathetic and parasympathetic system on the dilator and sphincter muscle of the iris. Modafinil increases pupil diameter as it increases the central sympathetic tone or decreases the central parasympathetic tone or both (Moro et al., 1981).

Light reflex can help us understand the mechanism by which modafinil causes pupil diameter to increase. It is already known that the amplitude of light reflex (constriction of the pupil after a light stimulus) depends on the number of neurons that

will be activated in the Edinger-Westphal nucleus (EW). The brighter the stimulus the greater the number of neurons that will activate EW and the greater will be the activation of the sphincter muscle and the constriction of the pupil. Every inhibition of the EW activation causes a decrease in the amplitude of the light reflex. The activity of hypothalamic regions and the sympathetic chain that results on the dilator muscle cause the pupil to return on its initial amplitude, after its constriction. Everything that increases the sympathetic tone also increases the time that the pupil needs so as to return at its initial diameter (Moro et al., 1981; Hutchings & Holly Field, 1984).

Our finding that modafinil reduced the amplitude of the reflex but did not affect the returning of the pupil on the 75% of its initial diameter proves that the drug acts on EW nucleus by increasing its inhibition, whereas it does not increase sympathetic system originating from hypothalamus. The absence of affection of modafinil on the sympathetic tone was also proved by its lack of effect on cardiovascular parameters. This finding is in agreement with bibliography, where it is referred no sympathomimetic and cardiovascular action of the drug, instead of the fact that it enhances alertness (Moldofsky et al., 2000; Mitler et al., 2000).

Modafinil improved the time of reaction on the simple reaction time test (RTI), and especially on the reaction visual information processing test (RVIP), where it also improved accuracy and information processing. Because these tests depend on mechanisms that induce alertness, our findings seem to be consistent with the alerting property of the drug (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000; Moldofsky et al., 2000). Modafinil did not seem to affect significantly mechanisms of selective attention and inhibition of responding (Stroop Test), neither of working (SSP) and recognition memory (PRM). Modafinil seemed to increase the time that patients needed to plan their moves at the Stockings of Cambridge (SoC) test, so they were faster and gave more correct answers. Because of the fact that this problem-solving test depends on the activation of prefrontal cortex (Cazalis et al., 2003; Dagher et al., 1999), it is difficult to understand whether action of modafinil is affected by activation of the dorsolateral prefrontal cortex or other regions that enhance alertness.

Thus, modafinil has been shown to reduce central parasympathetic activity, whereas causing no effects on central sympathetic activity (lack of effect on pupillary and cardiovascular indices of sympathetic system). It has been also shown to increase subjective alertness and improve cognitive functions that depend on wakefulness.

Actions of modafinil on alertness, cognitive function and pupil are consistent with what is already known about the mechanism of its action on the CNS. Modafinil activates orexin-A neurons on the lateral hypothalamic area, which activates the histaminergic neurons of the tuberomammillary nucleus (TMN) at the posterior lateral hypothalamus, directly and indirectly by activating a GABAergic inhibitory mechanism from VentroLateral PreOptic area (VLPO). TMN neurons innervate the cortex with ascending histaminergic excitatory neurons, while with descending neurons activate (together with descending orexin neurons) the monoaminergic pathways of brainstem, mostly the noradrenergic nucleus locus coeruleus, and also the raphe nucleus and the pons' cholinergic neurons (Lin et al., 1996; Chemelli et al., 1999; Scammel et al., 2000; Huang et al., 2001; Tashiro et al., 2002). Activation of locus coeruleus is believed to be the central mechanism of the drug for activating the cortex and for affecting the pupil size. Specifically, ascending noradrenergic neurons from locus coeruleus activate the a_1- and b- adrenergic post-synaptic receptors that later play a permissive role on the excitation of the inhibitory 5-HT receptors that inhibit GABA release from subcortical neurons. This reduction of GABAergic neurotransmission in the cortex and other regions, which are either related or not with sleep, is probably the basic mechanism for the alerting effect of the drug (Tanganelli et al., 1992, 1994, 1995; Ferraro et al., 1996b; Lin et al., 1996; Rush et al., 2002a). On the other hand, ascending noradrenergic neurons from locus coeruleus tonically inhibit the parasympathetic nucleus of EW, which results in the reduction of pupil constriction and increase of pupil diameter (Szabadi & Bradshaw, 1996). The fact that EW nucleus is thought to be the main part for the production of pupillary light reflex, explains our finding that modafinil causes inhibition of the light reflex after a bright light stimulus.

Thus, our findings are in complete agreement with the already known role of locus coeruleus in alertness, by its interaction with the cortex and the centre of pupillary light reflex, and with what is already known about the actions of modafinil.

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