# The association between sleep self-assessment and cognitive and psychomotor performance in medical students

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Master's thesis / Diplomski rad

2021

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet

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# UNIVERSITY OF SPLIT SCHOOL OF MEDICINE

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# THE ASSOCIATION BETWEEN SLEEP SELF-ASSESSMENT AND COGNITIVE AND PSYCHOMOTOR PERFORMANCE IN MEDICAL STUDENTS

#### **DIPLOMA THESIS**

Academic year:

2020/2021

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Split, July 2021

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#### **ACKNOWLEDGEMENT**

Foremost, I would like to express my sincere gratitude to my mentor Assist. Prof. Ivana Pavlinac Dodig, MD, PhD providing me with help, enthusiastic encouragement and valuable and constructive suggestions for my thesis. Her great knowledge, guidance and motivation has been indispensable for me writing my diploma thesis. I would also like to thank the department of Neuroscience for letting me use their data.

I wish to acknowledge the support and encouragement of my fellow colleagues and friends, who made my student times not only more productive, but also more enjoyable and becoming a second family to me during the last six years.

Finally, I want to express my gratitude to my family for their love and exceptional support during these studies. Thank you for supporting me in becoming a doctor.

#### **List of Abbreviations**

NREM – Non Rapid Eye Movement

REM – Rapid Eye Movement

EEG – Electroencephalogram

EMG – Electromyography

ARAS – Ascending Reticular Activating System

SWA – Slow-Wave Activity

SCN – Suprachiasmatic Nucleus

RHT – Retinohypothalamic Tract

CBT – Cognitive Behavioral Therapy

RBD – REM sleep Behavior Disorder

OSA – Obstructive Sleep Apnea

AHI – Apnea-Hyponea Index

CSA – Central Sleep Apnea

RLS – Restless Leg Syndrome

ESS – Epworth Sleepiness Scale

STOP-BANG – STOP-BANG questionnaire

SSS – Stanford Sleepiness Scale

PVT – Psychomotor Vigilance Test

CRD – Computer-based system Complex Reactionmeter Drenovac

MinT – Single task solving time

TTST – Total Test Solving Time

#### 1.1 Sleep

About 1/3 of our life we spend sleeping. Although it was long time thought that sleep is a passive process we now know that it is a neurophysiological process including many parts of our brain. We know that a good sleep quality is essential to maintain our brain functions. When we are awake, we are conscious about sensory stimuli. On the contrary, sleep can be described as a state with an absence or reduction of movement, reduced responsiveness to external stimuli, closed eyes, recumbent body position (1).

It is thought that sleep facilitates the regulation of somatic and neuronal growth, memory consolidation, thermoregulation and energy conservation (1).

New studies are suggesting a relationship between inadequate sleep, hypertension, obesity, type 2 diabetes mellitus, impaired immune functions, cardiovascular diseases, arrhythmias, mood disorders, neurodegeneration and dementia (2), kidney diseases, chronic obstructive pulmonary disease (3). Good sleep on the other hand appears to improve the long-term prognosis of individuals with tension-type headache, migraine and chronic musculoskeletal pain, while inadequate sleep increases the risk for new onset cases of chronic pain in pain free individuals (4).

Sleep is essential for the processing of new memories. In Non Rapid Eye Movement (NREM sleep) the hippocampal neocortical circuits are reactivated. These circuits play an important role in the wake learning period. In Rapid Eye Movement (REM sleep) the consolidation into long term memories takes place and there seems to be an association between REM sleep and creative behaviors. Children with a good sleep seem to have a better language and cognitive development.(5)

Neuroimaging shows an association between sleep deprivation and a greater magnitude of the activation of the amygdala. Together with a diminished amygdala-prefrontal connectivity it induces a lack of cognitive control (5).

Hypertension and arrhythmias seem to be related to the altered autonomic nerve activities in people with sleep deprivation. Furthermore, the altered humoral factors in sleep deprivation seem to play a role in sleep deprived associated hypertension. Paradoxical sleep deprivation also produces damage to cardiac structure and function which is also likely due to the automatic dysfunction. (5)

Sleep restriction is also favoring metabolic disease. In sleep deprived individuals the glucose metabolism is decreased. The glucose tolerance is due to the altered alpha and beta cell function while the leptin levels are decreased and the ghrelin level are increased. This metabolic changes lead to a high risk for the development of diabetes. Sleep deprivation can be described

as a catalyzer for metabolic dysfunctions. Sleep deprivation is also associated with an instability in the immune system and thereby associated with a higher rate of infectious diseases due to a higher sustainability to microbes (6).

#### 1.2 Sleep stages

There are two different types of sleep: the REM sleep and the NREM sleep. The NREM sleep can be further subdivided into 3 stages: stage 1, stage 2 and stage 3. All stages are associated with specific neuronal activity, which can be differentiated on the electroencephalogram (EEG) (1). During sleep we cycle through all stages of non-REM and REM sleep for approximately three to five times. During the morning we tend to have increasingly longer, deeper REM periods (7).

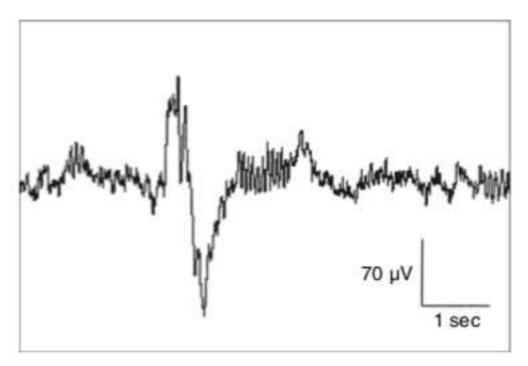
Stage 1 of sleep is characterized by low-voltage, mixed frequencies and prominent theta activity on the EEG. Approximately 50% or more of the EEG is occupied by alpha activity. The absence of sleep spindles or K complexes is indicative for stage 1 of NREM sleep and vertex sharp waves may be present in this stage. In the EMG a high chin muscle activity can be observed. In general, this stage is a transitional phase from wakefulness to sleep and accounts for about 2-5% of the total sleep time in adults.

In stage 2 of NREM sleep low voltage mixed-frequency activity and the presence of sleep spindles and K complexes can be observed. In the EMG a low chin muscle activity can be observed (1). The temperature drops and the muscles relax and we can observe slowed breathing and pulse. The eye movement stops. In the first cycle stage 2 lasts for 10-25 minutes and each time stage 2 prolongs during the night. About 50% of the night we spend in stage 2 (7).

Stage 3 of NREM sleep is characterized by more than 50% of delta waves in the EEG and the presence of sleep spindles. The muscle tone, pulse and breathing rate decrease in N3. In the beginning of the night N3 stages are about 20-40 minutes long and they tend to shorten and become replaced by REM sleep in later cycles. N3 seems to be important in recovery, growth and a functional immune system (7).

REM sleep is characterized by 2 phases: the tonic and the phasic phase. In the tonic phase we don't expect rapid eye movements which will than occur in the phasic sleep. The EEG is composed of the low voltage and mixed frequencies, especially theta and beta rhythms, sawtooth waves and alpha waves being 1-2 Hz slower than those occurring in NREM stage 1. In the tonic REM sleep there are no eye movements while rapid eye movements are observed in

phasic REM sleep. In comparison to NREM sleep, the chin EMG is reduced or absent and a loss of postural muscle tone due to postsynaptic hyperpolarization of the spinal motoneurons can be observed. In one night we usually experience three to five periods of REM sleep, which progresses towards the latter part of sleep. The NREM and REM sleep stages cycle every 90 to 120 minutes throughout the night in an adult. In REM stage we experience generalized skeletal muscle atonia and an increase in middle ear muscle activity in the phasic sleep. In the phasic REM sleep the sympathetic tone is increased. The respiratory pattern is irregular causing a decrease in tidal volume. There is a decrease in hypoxic and hypercapnic ventilatory response and decrease in activity of the upper airway dilator muscles. During REM sleep the brain metabolism and temperature are increased and a fluctuating pulse and blood pressure can be observed (1). REM sleep seems to be essential for cognitive functions like memory, learning and creativity. In REM stages we experience vivid dreams (7).



**Figure 1.** K complex with following sleep spindle (From A Review of Sleep EEG Patterns.

Part I: A Compilation of Amended Rules for Their Visual Recognition according to

\*Rechtschaffen\* and Kales\*

Andrea Rodenbeck, Ralf Binder, Peter Geisler, Heidi Danker-Hopfe, Reimer Lund, Friedhart Raschke, Hans-Günther Weeß, Hartmut Schulz Chairman Pages: 159-175First Published: 31

October 2006

#### 1.3 Sleep neurophysiology

The ascending reticular activating system (ARAS) seems to play an important role in the regulation of sleep. It includes the dorsal raphe nuclei, the ventral tegmental area, the locus coeruleus, the laterodorsal tegmental peduculopontine nuclei which release serotonin, dopamine, noradrenalin and acetylcholine, respectively.

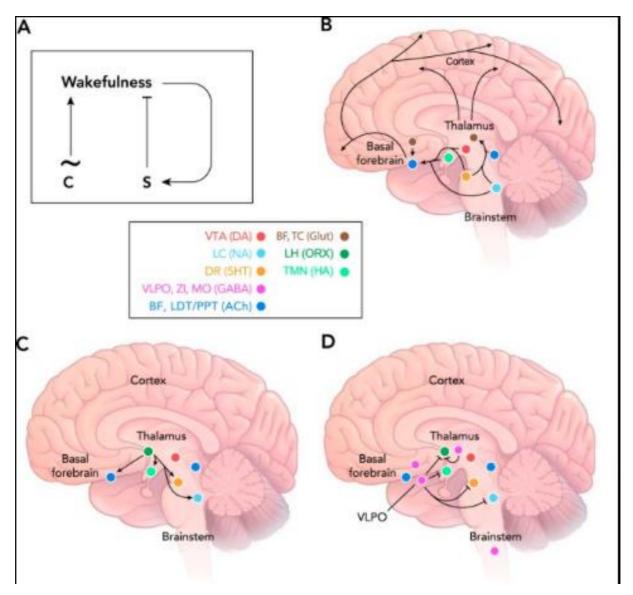


Figure 2. Neuroanatomy of sleep control (see text 1.3 for more information)
From Joiner WJ. The Neurobiological Basis of Sleep and Sleep Disorders. Physiology
(Bethesda). 2018;33:317-27.

The dorsal pathway modulates the thalamus, while the ventral pathway goes to the basal forebrain. Both pathways finally project to the cortex. The ventral pathway furthermore contains the lateral hypothalamus and the tuberomamillary nucleus releasing orexin and histamine. Orexin plays an important role in the enhancement of many arousal promoting nuclei and thereby stabilizing the arousal phase. In NREM sleep cholinergic and monaminergic signaling are both reduced causing dampened cortical excitation and increased filtering of sensory information at the level of the thalamus. The GABA-ergic neurons within the cortex, the brainstem, the ventrolateral preoptic nucleus, the basal forebrain and the subthalamus suppress arousal. Theses circuits cause REM and NREM sleep with oscillations in the sleep stages caused in the brainstem. The sleep promoting loci seem to form inhibitory connections with arousal promoting loci causing a rapid transition (8).

#### 1.4 Regulation of sleep

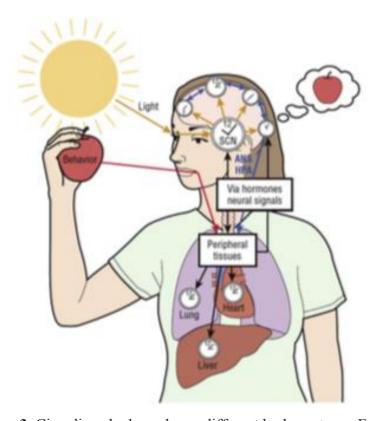
In 1982 two internally driven processes were described, which regulate the sleep-wake cycle. The sleep-wake cycle is composed of a homeostatic sleep-dependent process (process S), and a circadian, sleep independent process (process C).

Process C is the wake promoting part of the circadian clock, which works in a 24h cycle manner. By the interaction of the circadian process with the hemostatic process we are able to be awake during the day and sleep during the night (9). The cortical activity is more influenced by a combination of sleep propensity changes and the circadian rhythm while the subcortical region is mostly influenced by the circadian system (10).

Sleep homeostasis describes the compensatory mechanism by which the intensity and the duration of sleep are increased after sleep deprivation, while excessive sleep causes less deep sleep (11). In order to measure the NREM sleep depth, the slow-wave activity (SWA) is determined. A high arousal threshold is associated with a higher SWA (9). SWA is higher after previous sleep deprivation and declines for example in someone who has taken naps (10). The homeostasis also regulates the deprivation of certain phases of sleep. After a REM sleep deprivation, the following sleep will have extended periods of REM sleep in the cycles. The NREM-REM cycle causes a reduction in NREM sleep in this case and vice versa (9).

The circadian rhythm is responsible for the temporal management of different organ systems. The area in the brain, which controls the human circadian rhythm is the suprachiasmatic nucleus (SCN), which is part of the anterior hypothalamus. The SCN is

sensitive to light receiving inputs from the retina via the retinohypothalamic tract (RHT) (8). The SCN efferents address the basal forebrain and diencephalon by both neural efferent and paracrine signals. The SCN also seems to have indirect effects on the circadian rhythm. It does not only cause rhythmicity in downstream peripheral clocks via neural and neuroendocrine signals, but also controls rhythmic feed, activity and other behavioral, physiologic and cellular mechanisms. Thereby all external and internal stimuli are temporally coordinated in one big system (12).



**Figure 3.** Circadian clock works on different body systems. From Rosenwasser AM, Turek FW. Neurobiology of Circadian Rhythm Regulation. Sleep Med Clin. 2015;10:403-12.

The circadian system also influences the mental health including psychiatric diseases, like depression and bipolar disorder and neurodegenerative disorders like dementia. New studies suggest a correlation between the circadian rhythm and DNA repair process, which are involved in the prevention of cancer. There seems to be a connection between the circadian cycles and the influence of anti-cancer drugs. (13)

Without a proper signaling from the SCN pacemaker we can expect several consequences including insomnia, excessive daytime sleepiness, and impaired sleep quality

(13). There are different circadian rhythm sleep-wake disorders categorized on their characteristics and causes.

The jet lag disorder occurs in people who cross the time zones multiple times in a short period of time. This disorder is usually temporary and resolves when the person changing the time zone, adjusts to the day-night cycle of the new location. This disorder is characterized by sleeping problems and fatigue. Different groups of people who suffer from disruptions in circadian rhythms are people working in night shifts. The advanced sleep disorder makes people tired in the very early evening while it wakes them up in the very early morning. This disorder affects only around 1% of people in middle and older age. On the contrary, the delayed sleep phase disorder causes people to wake up late in the morning and fall asleep late in the evening. It is very rare in the general population but appears in up to 16% of teens. (13)

Blind people are not able to receive light-based stimuli for their circadian rhythm. Although their body is still following a 24h based cycle, there is a constant backward shift in their sleeping time. Associated with neurodegenerative disorders, which affect the SCN, we can find the irregular sleep-wake rhythm disorder, which is characterized by many short sleeping periods throughout a 24h cycle (13).

#### 1.5 Sleep disorders

Sleep disorders can influence all body functions (14). The majority of sleep disorders remain undiagnosed. These disorders have an effect on the overall health, safety and performance outcomes (15). Patient having sleep disorders may experience irregular breathing, daytime sleepiness, increased movements during sleep, irregular sleep cycles, trouble falling asleep and behavioral problems (14).

#### 1.5.1 Insomnia

Insomnia is defined as a disorder characterized by problems falling asleep and/or staying asleep or experiencing nonrestorative sleep (16). About 1/3 of the adult population experiences transient insomnia at least once in their life, out of these, 40% develop into chronic patients (17). Woman and older adults are affected more often, with woman being affected most often at the onset of menses and menopause (16). The diagnosis is made according to the patient reports on decreased sleep. The disorders can be further subdivided into sleep onset and sleep maintenance insomnias (17). The newest classification, from the International classification of

sleep, describes the short-term, chronic and other insomnias (18). The most common signs of insomnia reported by patients are daytime sleepiness, impaired attention, and mood disturbances. The diagnosis of insomnia is set when there are problems for at least three nights per week and those problems last at least 3 months (17). Factors contributing to the development of insomnia include behavioral, cognitive, emotional, or genetic factors (17). Comorbid medical disorders, psychiatric disorders, and working on night rotating shifts significantly increase the risk of developing insomnia. The most commonly associated disorders are psychiatric, with depression being the most common of these.

Insomnia is characterized by a state of hyperarousal, which is experienced throughout the entire day. It causes a hypervigilance during the day accompanied by a difficulty to initiate sleep and maintain sleep at night. The pathophysiology can be explained by two different models: the cognitive model and the physiological and neurophysiological model.(16) The cognitive model describes the worry and rumination about falling asleep. On the physiological and neurophysiological level patients with insomnia have a higher metabolic rate. The heart rate is increased in insomnia patients as well as the urinary free cortisol. (16) The glucose metabolism during waking and REM episodes is also increased in patients with insomnia compared to patients with good sleep (16). Since over 100 years' scientist suspect an association between depression and sleep deprivation. Although it was often thought that insomnia is caused by the depression, this relationship seems to be bidirectional. Thus, insomnia itself is also used as a predictor for depressive disorders (19).

Treatment of insomnia includes the establishment of good sleep habits like keeping regular wake times, staying in bed only for sleep, avoiding afternoon consumption of caffeine and alcohol, avoiding nap during the daytime (and if only for under 30 minutes) (17). The first line therapy for insomnia is cognitive behavioral therapy (CBT), but since there is a lack of providers, digital form of cognitive behavioral therapy is increasingly used (18). The CBT is using sleep restriction and stimulus control as therapeutic measures. Sleep restriction should cause an increase in sleep drive. Sleep restriction should not be used in patients who have a tendency to develop seizures and obstructive sleep apnea patients. The stimulus control part of the CBT is supposed to break the association between lying in bed and negative aspects of insomnia. Patients should stop to connect the bed with wakefulness, frustration, worries but to establish a connection between bed and sleep (18).

In patients with short term insomnia or just as an addition to CBT pharmacological therapy can be considered. Thereby the type of complain, the frequency of insomnia symptoms, the length of the treatment and the patient's age and comorbidities should be taken into

consideration. Insomnia presenting with sleep initiation problems is best treated with short-acting medications, while sleep maintenance problems are best treated with long-acting medications like eszopiclone. Depressive and anxious patients can be treated with antidepressant therapy. In general, most frequently used medications are benzodiazepines, which are cheap and broadly available, but they have a number of side effects including a high sedative effect and the development of tolerance. Zolpidem is often used as well but is associated with a high sedative effect and the development of parasomnias (17).

#### 1.5.2 Parasomnias

Parasomnias are a group of sleep related behavioral disorders which are experienced during sleep or in the transitional phase of sleep and waking up. They may occur alone or in combination with other disorders like trauma other psychiatric illnesses, other sleep related disorders and neurological disorders like Parkinson and spinocerebellar ataxia (Shantanu). Parasomnias can be divided into three groups:

- 1) NREM related parasomnias
- 2) REM related parasomnias
- 3) other parasomnias (20).

#### 1.5.2.1 NREM related parasomnias

NREM parasomnias are characterized by incomplete episodes of awakening. Usually individuals experience amnesia of the event, and they don't response to people from the outside intervening (20).

#### Confusional arousals

Confusional arousals are also called Eleanor syndrome (21). They are associated with mental confusion, amnesia and may include automatic behaviors like mumblings and motor activities, while ambulation and sympathetic over-activity are absent. These disorders are usually benign and are more common among the pediatric population (22).

#### Sleep walking

This parasomnia is primary characterized by the ambulatory behavior (22). The patient is disorientated with open eyes and can be aimlessly wandering around while also playing an instrument, urinate, or even cause dangerous situations like driving or jumping from the balcony. Therefore, it is important to include the family and cause a safe environment during sleep for individuals with this disorder (21). This type of parasomnia is associated with other sleep disorders like restless leg syndrome, obstructive sleep apnea, febrile illness, migraines, strokes, chronic pain syndrome and the use of hypnotic medications (21/22).

#### Night terrors

People suffering from night terrors usually arouse suddenly screaming and crying in fright and are not responsive to outside stimuli (22). These episodes last between 30 seconds and 30 minutes (20). The motor and automatic activity are hyperactive and therefore cause: tachypnea, tachycardia, mydriasis and diaphoresis (21). The majority of individuals don't have any memories of the event or the source of their fear (20).

#### 1.5.2.2 REM related parasomnias

#### REM sleep behavior disorders

Individuals with REM sleep behavior (RBD) disorder often experience unpleasant dreams and act out vivid with wild arm and leg movements during REM sleep (23). In contrary to normal REM sleep which is characterized by atonia, in RBD individuals have an increased muscle tone and/or phasic muscle twitching during REM sleep (24). We can differentiate between RBD and secondary RBD which is associated with neurodegenerative diseases (25). The pathophysiology of RBD is not yet fully understood but neuropathological studies have found neuronal loss and Lewy bodies in brainstem nuclei, which regulate REM sleep atonia (26). Idiopathic RBD (iRBD) can be used as a predictor of neurodegenerative disease. It is thought that RBD can manifest before the onset of motor and cognitive functions loss. RBD can be diagnosed with screening questionnaires and polysomnography. The treatment of RBD includes the treatment of the underlying cause, creating a safe sleep environment and pharmacotherapy with clonazepam or melatonin (25).

#### Nightmare disorder

Individuals with the nightmare disorder experience recurrent vivid dreams including threats to survival or security. The disorder is therefore accompanied by fatigue, distress and reduced cognition. It is often associated with post-traumatic stress disorder and limitations in motor activity (13). During childhood nightmares are very common and usually children can remember their dreams very well. It often resolves spontaneously in children and should only be diagnosed if the problems persist (22).

#### 1.5.3 Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a sleep disorder in which nocturnal breathing cessation occurs due to upper airway collapse (27). The breathing interference consequently causes recurrent episodes of nocturnal hypoxemia, hypercapnia, endothelial dysfunction, hypercoagulability and sympathetic over-activity (28). Since the sleep is nonrestorative, patients experience daytime somnolence (27). OSA appears due to a diminished space for airflow through the upper airway. Common anatomical reasons for OSA include micrognathias, retrognathia, facial elongation, mandibular hypoplasia, adenoid and tonsillar hypertrophy. Nonanatomic and most common risk factors of OSA are central fat distribution, obesity, advanced age, male gender and alcohol abuse (27). OSA should be suspected if the patient is snoring, experiences daytime sleepiness and suffers from early morning headache (29). All patients with common risk factors and diseases which co-occur with OSA should be assessed with the screening questionnaires (30). The diagnostic method of choice is a whole-night polysomnography, which determines the number of respiratory events per hour of sleep. expressed as apnea-hypopnea index (AHI). The diagnostic criteria for setting the diagnosis of OSA are at least 5 events per hour. In cases of an AHI from 5 to 14, mild sleep apnea is considered, from 15-19 it is considered moderate sleep apnea and 30 events or more per hour of sleep it is a severe sleep apnea (17).

Untreated OSA has an influence on almost all body functions. It is connected to higher risk of cardiovascular complication like hypertension, myocardial ischemia, heart failure and stroke (28), as well as cognitive deficits (17).

The treatment of OSA depends on the severity of the disease. For mild OSA conservative therapies like weight loss and avoiding supine position in positional sleep apnea might be sufficient. In general, the first line treatment is continuous positive airway pressure therapy. It reduces symptoms like daytime sleepiness and mood disturbance and improves

cognitive functioning and thus increases the total quality of life. In some cases, the surgery of the soft palate, nasal surgery and maxilla-mandibular region might be indicated (17).

#### 1.5.4 Central sleep apnea

In central sleep apnea (CSA) the drive to breath during sleep is not sufficient causing decreased or absent ventilation and consequently a lack of gas exchange. Such as in OSA, central apnea patients experience daytime sleepiness, have increased risk of cardiovascular events (31) and insomnia (32). The CSA is defined as cessation in airflow of 10 or more seconds without respiratory effort. The diagnostic criteria for CSA are fulfilled if 50% or more respiratory events are central in origin (32). CSA syndromes can be either hypercapnic or nonhypercapnic. Hypercapnic patients have an increased daytime PaCO<sub>2</sub> which is rising further in sleep. Congenital central hypoventilation syndrome, tumors or trauma compressing the brainstem, opioid-induced sleep disorder and a wide range of neuromuscular disorders are the most common causes of hypercapnic CSA. Nonhypercapnic CSA is mostly observed in patients with congestive heart failure. The treatment of CSA has to be adjusted to the cause of the apnea (31).

#### 1.5.5 Restless leg syndrome

Restless leg syndrome (RLS) is a neurological disorder affecting around 10% of the adult population and is more common in females. The exact pathophysiology is not fully understood but a relationship between dopamine and iron dysfunctions in the central nervous system was observed in patients with RLS (33). It is thought that iron dysfunction has an effect on the dopaminergic system and opioids might have a protective effect on the dopaminergic system. In RLS the body moves in order to get a relief from the paresthesia-dysesthesia feelings, which appear mainly while being at rest. Patients seek for help mostly due to insomnia, since the symptoms significantly worsen towards the evening and are less pronounced in the morning after waking up (34,35).

Periodic limb movement can be observed in more than 80% of patients (36). The diagnosis is mostly a combination of the anamnesis and the exclusion of other causes. The treatment includes life style changes, like avoiding tobacco and alcohol use as well as maintaining a good sleep pattern, moderate exercise and massaging the legs. In case iron is depleted, supplementation is indicated. Antiseizure drugs like gabapentin and dopaminergic

agents seem to improve the condition. Further research is needed to be more certain about the exact mechanism leading to the diseases and thereby improving the treatment options (36).

#### 1.5.6 Screening tests for sleep disorders

#### 1.5.6.1 Epworth Sleepiness scale

The Epworth sleepiness scale is a self-administered questionnaire, to measure daytime sleepiness (37). The ESS contain 8 different daily situations in which the participant should evaluate their likelihood of falling asleep (38). Each scenario can be evaluated with a 4 points scale (from 0 to 3, with 0 representing minimal, and 3 maximal chance to fall asleep) and the total score (obtained as a sum of all 8 scores) can be maximally 24. A score up to 10 is considered normal while a score above 10 indicates further diagnostic procedures. (39) The ESS is used for a large diverse clinical population. Studies shows that the ESS will provide an accurate measure of daytime sleepiness in different study groups, like young medical students or patients suffering from severe apnea (40).

#### 1.5.6.2 STOP-BANG questionnaire

The STOP-BANG (stands for Snoring. Tiredness, Observed apnea, Pressure, Body Mass Index, Age, Neck circumference and Gender) questionnaire was developed as a screening tool in preoperative screening of OSA patients (30). The questionnaire contains eight dichotomous items which are associated with sleep apnea. The patients can be classified according to a score from 0-8. A score from 0-2 is considered a low risk of OSA. As it is easy to use has, efficient and has a high sensitivity, it is often used in sleep medicine (41).

#### 1.5.6.3 Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) was developed in 1988. It is one of the most commonly used sleep screening questionnaires. It gives reliable, valid and standardized measures of sleep quality, differentiates good quality sleeping individuals, to those who have a worse sleep and is widely available (42).

#### 1.5.6.4 Stanford sleepiness scale (SSS)

The Stanford sleepiness scale (SSS) is used for the assessment of subjective sleep quality during the day at particular time point (43). The scale ranges from 1 (feeling active, awake and vital) to 7 (sleep onset soon, no longer fighting sleep, and having dream-like thoughts). A higher SSS scores means a higher level of sleepiness in the subjects. The SSS was used in combination with cognitive tests, since it has been found to predict vigilance and reaction time (44).

#### 1.5.6.5 Berlin questionnaire

The Berlin questionnaire was developed 1996 in Germany for the use among the primary care population and contains 10 questions (45). These focus on the presence and severity of snoring, apnea, daytime sleepiness, obesity and hypertension (30).

#### 1.6 The importance of sleep in cognitive functioning

There is large consensus that sleep deprivation has an effect on a number of different cognitive functions, but the exact mechanisms by which sleep is becoming essential is still part of scientific work. Getting a better understanding of the sleep functions in cognitive functioning can improve the health of many workers with sleep deprivation (46). Most often the performance of the working and long-term memory, the visuomotor and verbal functions and decision making are determined. Two different theories are used to describe the different mechanisms of cognitive functions. The first one is focusing on the general effectiveness on alertness and attention while the second one describes the selective effects on certain brain structures and functions. The general theory is based on the two-process model of sleep regulation. Disabilities in attention are influenced by lapses, slowed responses and wake instability while cognitive impairments are mediated by decreased alertness. The main reason for a diminished cognitive performance are so called attentional lapses, and are brief moments of inactiveness. In individuals with sleep deprivation the number of attentional laps increases and small episodes of microsleep can be observed in the EEG (46). The wake state hypothesis describes the oscillation in alertness and effort.

The second part of the two-process model describes the diminished functions in specific brain region. Horne developed the prefrontal vulnerability hypothesis, which describes the impairment of cognitive functioning relying on the prefrontal cortex. These include higher functions like language, executive functions, divergent thinking and creativity. In order to test these functions a complex test, which is new to the examined person, should be developed.

The working memory can be subdivided into the phonological, visuospatial sketch pad, episodic buffer and central executive system. The phonetical system is a temporary reservoir of verbal and acoustic information. It is therefore also called the echo memory. The iconic memory contains the visuospatial information, while the episodic buffer combines information from different sources. The executive process, which is thought to be responsible for sustaining attention, is controlling all systems of the working memory. (47)

The psychomotor vigilance test (PVT) is the most common used to determine the loss in vigilance. The test is sensible to sleep loss effects and provides information about reaction speed and lapses (47). The performance in reaction time and accuracy declines after 16h of wakefulness and worsens continuously into the early morning. In general, sleep deprivation leads to slowed response time in the PVT. Dawson and Reid performed a study in 1997 comparing various blood alcohol concentrations with sleep deprivation on a simple hand-eye tracking test. The results showed an equivalent performance of someone being 24h awake to the performance of an individual with 0.10%, which is considered intoxicated in the USA (46). The performance on the ability to perceive visual stimuli has been a topic of scientific work in the previous years (46). Visual-motor performances are measured by tasks of digit symbol substitution, letter cancellation, trail tracking or mace tracking. An impaired spatial attention is associated with a decreased functioning of the oculomotor system and consequently a decreased functioning of the visual performance (47). Sleep deprivation has shown and overall worsening of response omission on the entire field of visual perception (46). Rauge and Gabaude performed a study showing that a single night of sleep loss was sufficient to a diminished visual perception (47).

A different part of the cognitive functioning is the emotional processing. Research has shown that impairments on the higher level of cognitive processing like memory, judgement and decision making occur, caused by changes in emotional processing due to sleep deprivation. (46) Sleep deprivation also has an influence on self- measurements. Individuals being sleep deprived for two nights are more likely blaming others for hypothetical predicaments. Frustration, intolerance, un-forgiveness, being self-focused is much more common among sleep deprived individuals. While convergent thinking (solving a problem in the context of known information) does not seem to be diminished by two nights of sleep deprivation, divergent and innovative thinking is significantly diminished. The inhibitory control describes the ability to

inhibit inappropriate behavior. It is markedly decreased even at an early course of sleep deprivation.

Functional magnetic resonance imaging showed tonic reductions in task related activation of the anterior and ventrolateral cortex. Furthermore, a tendency to take riskier decision was seen after two nights of sleep deprivation (46).

#### 1.7 Computer-based system Complex Reactionmeter Drenovac (CRD)

The CRD test is used as a measure for solving simple and complex cognitive and psychomotor reaction time tests (48). It has been in use in the psychodiagnostic assessment for more than 40 years. The test is made of the software and four electronic instruments. It is not relying on language or different specific knowledge and can be used for all ages groups. The tests are made up of 38 standard tests. A test generator, which is included in the software, allows multiple retesting on the same subject, since the subject can't memorize the test. The simple arithmetic operations (CRD11) measures convergent thinking and solving and constructing mathematical tasks. The light signal position discrimination (CRD311) measures detection, perceptive abilities and visual and spatial orientation. Complex psychomotor coordination (eyehand-leg) (CRD411) measures complex reaction times (49).

# 2. AIM AND HYPOTHESES

#### The aims of this thesis are:

- To compare cognitive and psychomotor performance between men and women who are medical students from the University of Split School of Medicine (USSM).
- To compare daytime sleepiness assessed with Epworth sleepiness scale (ESS) and Stanford sleepiness scale (SSS), subjective sleep quality assessed with Pittsburgh sleep quality index (PSQI) and sleep habits between men and women who are medical students from the USSM.
- To investigate the association between cognitive and psychomotor performance on three
  tests of the computer based system Complex Reactionmeter Drenovac (CRD-series), and
  daytime sleepiness assessed with ESS and SSS and subjective sleep quality assessed with
  PSQI in medical students from the USSM.

#### Hypotheses:

- Men will have shorter reaction times than women on three tests (CRD11, CRD311 and CRD411) of the CRD-series.
- Women will have shorter sleep duration and worse sleep quality assessed with PSQI than
  men, but there will be no difference in daytime sleepiness assessed with ESS and SSS
  between men and women.
- There will be negative correlation between daytime sleepiness assessed with ESS and SSS and performance on the tests of the CRD-series.
- There will be a positive correlation between sleep quality assessed with PSQI and performance on the tests of the CRD-series.

3. SUBJECTS AND METHODS

#### 3.1 Subjects

The cross-sectional study included 168 participants in the age ranging from 19 to 25 years. The participants where students enrolled in the Basic Neuroscience course during second academic year at the University of Split School of Medicine (USSM). The tests were performed during a practical called 'Reflexes and Reaction time'. The response rate was 100%.

#### 3.2 Methods

During the practical the students were given questionnaires to determine their sleepiness. We used the Epworth Sleepiness scale (ESS) and the Stanford Sleepiness Scale (SSS) to evaluate excessive daytime sleepiness, the Pittsburgh sleep quality index (PSQI) to evaluate quality of sleep and a questionnaire on sleep habits. Afterwards we informed the subjects about the purpose of the psychomotor testing and gave instructions and then performed the CRD battery testing.

#### 3.2.1 Questionnaires

The Croatian version of the Pittsburgh sleep quality index (PSQI) was used to assess the students' subjective sleep quality. The PSQI consists of 19 items which generate 7 component scores on sleep latency, disturbance, duration, habitual, quality and daytime dysfunction. The score of each item is ranging from 0 to 3, resulting in a maximum score of 21. A higher score is associated with a worse sleep quality (50). The Epworth Sleepiness scale (ESS) was used in order to assess daytime sleepiness. Eight items are used for the assessment of sleepiness in daily situations. The scale ranges from 0-3 for each of this items. We used the Croatian version of the ESS. The Stanford Sleepiness Scale (SSS) was used in order to assess the participants' current sleepiness. The point is rating from 1 to 7, the higher number indicating a higher sleepiness (44). We used a sleep habit questionnaire to determine whether the patients were chronically tired (yes/no) and if they were waking up during the night (yes/no).

#### 3.2.2 Computer-based system Complex Reactionmeter Drenovac (CRD)

For the assessment of the psychomotor system and the cognitive functions we used the Computer- based Complex Reactionmeter Drenovac test (CRD). Out of the 38 standard tests we used three tests. The CRD 11 generates simple arithmetic operations and was used to assess

convergent thinking and the ability to calculate easy mathematical tasks like subtraction and summation. The participants were pressing the key in the bottom of the panel with their second digit of the hand in this test. The configuration consisted of two light diodes in the upper corner of the panel indicating the arithmetic operation, while the numbers demonstrated by 12 light diodes in the central part of the panel.

To assess the detection and identification as well as the observational abilities and visual perception we used the CRD311. At the bottom of the panel one of nine small light diodes lights up randomly. The key below the emitting diode must be pressed by the participant.

For the measurement of complex psychomotor coordination, the CRD411 test (eye-hand leg) was utilized. In this test the light is emitted by four electrodes in the center of the panel, structured in a way, that the top row buttons are controlled with the participants' hands while the bottom row buttons are controlled via a pedal with their feet.

The CRD11 and CRD411 consist of 35 tasks while the CRD311 is made up of 60 tasks. The participants all solve the same sequence of tasks.

#### 3.3 Data collection and statistical analyses

The single task solving time (MinT) and the total test solving time (TTST) were used as variables for speed and accuracy of reaction time (51).

The data were collected and summarized with the use of the Microsoft Excel program. Statistical analysis was performed in the MedCalc for Windows, version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium). Categorical variables were shown as numbers and percentages, continuous data as means  $\pm$  standard deviations, and age was shown as median and minimum and maximum. Comparison of categorical data between men and women was made using  $\chi^2$ -test, while Student's t-test was used for comparison of continuous data. The association between cognitive and psychomotor performance and data obtained from questionnaires was investigated using Pearson's correlation coefficient. A P < 0.05 was considered statistically significant.

# 4. RESULTS

A total of 168 medical students from the USSM were included in the research. 49 Men with a median age of 20, ranging from 19 to 25, and 119 women with a median age of 21, ranging from 19 to 23. The demographic data of the subjects are shown in Table 1.

**Table 1.** Demographic data of the subjects

	Total	Men	Woman		
	N=168	N=49 (29.2%)	N=119 (70.8%)		
Age	21 (20-21)	20 (20-21)	21 (20-21)		
Weight (kg)	69.09±13.18	84.57±10.59	62.63±7.62		
Height (cm)	175.34±9.12	$186.17 \pm 5.52$	$170.82\pm5.95$		
BMI (kg/m <sup>2</sup> )	22.33±2.81	$24.38 \pm 2.65$	$21.47 \pm 2.41$		
Smoking (yes)	29 (17.26)	8 (16.33)	21(17.65)		

Age is shown as median (IQR), smoking is shown an absolute and relative frequencies and other variables are shown as means  $\pm$  standard deviations. BMI= Body mass index.

Women spent significantly more time studying per day than men (Figure 4).

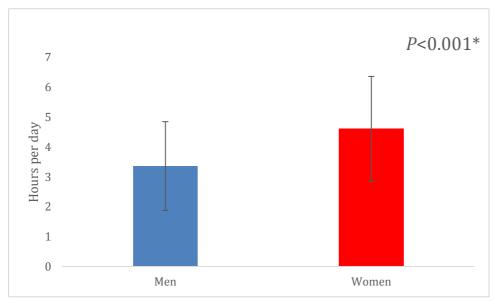


Figure 4. Time per day spent studying in men and women

<sup>\*</sup>Student t-test

The sleep assessment is presented in Table 2. In the PSQI there is a statistically significant higher score in women  $(5.68\pm2.53)$  compared to men  $(4.80\pm2.14, P=0.023)$ . The SSS score was also significantly higher in women in contrast to men  $(2.82\pm1.22 \text{ vs. } 2.23\pm0.98, \text{ respectively, } P=0.002)$ . Women also stated to sleep shorter  $(6h35min \pm 1h 8min)$  than men  $(6h 58min \pm 58 min, P=0.024)$ .

Chronic tiredness was significantly more frequent among women than men (P=0.007). A total of 56 women (47.06%) reported to be chronically tired compare to 12 men (24.49%) who stated to be affected by chronic tiredness. No significant differences among men and women was observed in the total ESS score (P=0.393), sleep latency (P=0.097), sleep time (P=0.560) and wake time (P=0.983). Furthermore, a similar proportion of men and women reported nighttime awakenings (P=0.457).

 Table 2. Sleep assessment

	Total	Men	Woman	P
	N=168	N=49	N=119	Γ
ESS total score	7.04±3.39	6.69±3.26	7.18±3.44	0.393*
PSQI total score	$5.42\pm2.45$	$4.80\pm2.14$	$5.68\pm2.53$	0.023*
SSS total score	$2.64 \pm 1.79$	$2.23 \pm 0.98$	$2.82 \pm 1.22$	0.002*
Sleep time	24h 5min ±	$24h \pm 1h 6min$	24h 7min $\pm$	0.560*
	1h 10min		1h 12min	
Sleep latency (min)	$16.74\pm12.84$	$14.50\pm9.78$	17.66±13.84	0.097*
Wake time	$7h 12min \pm 43min$	$7h\ 12min \pm 42min$	$7h 13min \pm 43min$	0.983*
Sleep duration	6h 41min ±	$6h 58min \pm 58min$	6h 35min ±	0.024*
	1h 6min		1h 8min	
Waking up, N (%)	26 (15.48)	6 (12.25)	20 (16.81)	$0.457^{\dagger}$
Chronically tired, N (%)	68 (40.48)	12 (24.49)	56 (47.06)	$0.007^{\dagger}$

<sup>\*</sup>Student t-test,  $^{\dagger}\chi^2$  test

Variables are shown as means  $\pm$  standard deviations, except Waking up and Chronically tired which are shown as an absolute and relative frequencies.

ESS=Epworth sleepiness scale total score. PSQI=Pittsburgh sleep quality index. SSS= Stanford sleepiness scale. Variables are shown as means  $\pm$  standard deviations.

In Table 3 the results of the CRD-series tests are shown. On the CRD11 test men had statistically significant shorter MinT and TTST (TTST  $94.46\pm14.84$  s and MinT  $1.61\pm0.23$  s) than women (TTST  $105.82\pm17.78$  s and MinT  $1.78\pm0.28$  s, P<0.001 for both comparisons). In the CRD411 men were also significantly faster than women (TTST  $26.94\pm4.76$  s vs.  $31.22\pm7.12$  s for TTST and  $0.30\pm0.07$ s vs.  $0.43\pm0.08$  s for MinT, respectively, P<0.001 for both comparisons). On the CRD311 test women needed significantly more time to complete the whole test than men (TTST was  $28.18\pm2.46$  s in women and  $27.43\pm2.09$  s in men, P=0.047). However, there was no difference in MinT between performance of women and men on the CRD311 test (P=0.257).

**Table 3.** Cognitive and psychomotor performance on the CRD-series tests

	Total	Men	Women	<b>P</b> *
	N=168	N=49	N=119	<b>F</b> "
CRD11				
TTST (s)	102.43±17.69	94.46±14.84	$105.82\pm17.78$	< 0.001
MinT (s)	$1.73\pm0.28$	$1.61\pm0.23$	$1.78 \pm 0.28$	< 0.001
CRD311				
TTST (s)	27.96±2.38	27.43±2.09	28.18±2.46	0.047
MinT (s)	$0.34 \pm 0.05$	$0.33 \pm 0.04$	$0.34 \pm 0.05$	0.257
CRD411				
TTST (s)	29.94±6.78	26.94±4.76	31.22±7.12	< 0.001
MinT (s)	$0.42 \pm 0.08$	$0.39\pm0.07$	$0.43 \pm 0.08$	< 0.001

<sup>\*</sup>Student t-test

Data are shown as means  $\pm$  standard deviations

CRD=Complex Reactionmeter Drenovac test; TTST=total test solving time, MinT=minimal signal task time.

Table 4 shows the correlation between the performance on CRD-series tests and sleepiness, assessed with the ESS and SSS, sleep quality assessed with PSQI, and subjective sleep duration. No significant correlation was found among investigated variables.

**Table 4.** Correlation between performance on CRD-series testing and sleepiness assessed with Epworth sleepiness scale and Stanford sleepiness scale, sleep quality assessed with Pittsburgh sleep quality index and sleep duration

	ESS		PSQI		SSS		Sleep duration	
	r	P*	r	P*	R	P*	R	P*
CRD11								
TTST (s)	0.042	0.589	0.038	0.625	0.071	0.360	-0.039	0.616
MinT (s)	0.096	0.216	-0.012	0.877	0.059	0.447	-0.033	0.671
CRD311								
TTST (s)	0.075	0.334	-0.060	0.440	0.007	0.928	-0.101	0.193
MinT (s)	0.060	0.440	-0.005	0.949	0.025	0.748	-0.121	0.118
CRD411								
TTST (s)	0.121	0.118	0.058	0.455	0.035	0.652	-0.122	0.115
MinT (s)	0.132	0.088	0.065	0.403	0.080	0.303	-0.131	0.091

<sup>\*</sup>P values were calculated for Pearson's correlation coefficient

CRD=Complex Reactionmeter Drenovac, TTST=total test solving time, MinT=minimum single task solving time, ESS=Epworth sleepiness scale total score, PSQI=Pittsburgh sleep quality index, SSS=Stanford sleepiness scale

# **5. DISCUSSION**

In our study we found a significant difference in the sleep quality and sleep duration measured with the PSQI and in daytime sleepiness measured with the SSS in men compared to women. Women had a higher score indicating a poorer sleep quality. The ESS showed no significant difference between daytime sleepiness in the two genders. A study from China has also shown a worse subjective sleep quality assessed with PSQI in women compared to men similar to our results (52).

Previously it has been reported that sleep problems are very common among students (53). In a large study conducted in the United States with college students from 6 different universities women reported to need more time to fall asleep than men and claimed to use more sleep medications in comparison to men (54). In a different study conducted on college students, women reported 2 times more stress related sleep problems. Furthermore, women are more prone to feel emotional stress which might cause repetitive thinking and consequently results in insomnia. Thus, it is not surprising that insomnia is more often among female students (53). Women are less overconfident and more self-disciplined and therefore often spend more time per day studying (55,56) but are also more likely to develop anxiety and depressive symptoms that might be associated with worse sleep quality (54). The gender-related differences in sleep have been reported not only in students, but in all age groups. The literature describes more sleeping problems in woman compared to man across all ages. Furthermore, it has been shown that one night of sleep might restore the waking EEG in men but not in women (47) This indicates that the underlying physiological response to sleep deprivation is different in women compared to men. Furthermore, sex hormones might play an important role in the regulation of sleep, but this is a subject of further studies (47).

In this study, we found that men were faster than women on the test of convergent thinking, test of discrimination of the light signal position and test of psychomotor coordination of the CRD-series. Previous studies showed a better performance in men on tests assessing spatial and arithmetical abilities while woman usually perform better on tests assessing verbal abilities (57). A study performed by Ardila examining the difference in cognitive performance in 5 to 6-year-old children showed only minor differences between boys and girls in performance indicating that cultural aspects might play an important role in the development of cognitive functions (58). However, it seems that beyond a strong gender influence on the cognitive performance, the educational level has also an important impact (57). Even though a sexual dimorphism of certain brain structures has been described in details, still doubtless determination of the gender cannot rely only on the brain morphology (59). Beside the anatomical differences, a component which is sometimes underestimated is the contribution of

the menstrual cycle to the cognitive functions. Different levels of estradiol and progesterol influence executive functions, spatial navigation, functional asymmetry and attention (59). In 2005 a study showed a significant decrease in cognitive performance of women when they were told that a previous study showed that they would perform worse in comparison to a group which went in the study without this influence (57). Already in school male students are asked much more questions in math and science classes and knowing about the cultural and social influence we should try to establish an environment which gives both genders the possibility to develop their cognitive functions equally (57).

We did not find a correlation between daytime sleepiness assessed with ESS and SSS and the performance of the tests of the CRD-series and between subjective sleep quality assessed with PSQI and performance on the tests of the CRD-series. These results are not in accordance with most of the literature. Lim and Dinges reviewed investigated effects of sleep deprivation on the cognitive performance measured with the psychomotor vigilance test. In sleep deprived individuals a slowed general response could be observed. Thus, response speed was described to be very sensitive to sleep deprivation (46) According to the literature, a single night of sleep loss was sufficient to reduce the visual perceptual sensitivity. On the other hand, convergent thinking tasks seem to have a smaller association to sleep deprivation than psychomotor vigilance (46).

Regarding the limitations of our study, we believe that the small sample size might be the reason for not distinguishing correlation between daytime sleepiness and the cognitive performance on the CRD-series. The individual need of sleep between the subjects and the individual performance on the cognitive function testing is providing a bigger bias in a smaller sample size. Furthermore, the students were all medical students from Croatia and possibly a bigger sample including students from many universities worldwide would provide different results.

# 6. CONCLUSION

- 1. Men had statistically significant shorter reaction times than women on three tests (CRD11, CRD311 and CRD411) of the CRD-series.
- 2. Women had shorter sleep duration and worse sleep quality assessed with PSQI than men and experienced more daytime sleepiness assessed with SSS but there was no difference in daytime sleepiness assessed with ESS between men and women.
- 3. There was no correlation between daytime sleepiness assessed with ESS and SSS and performance on the tests of the CRD-series.
- 4. There was no correlation between sleep quality assessed with PSQI and performance on the tests of the CRD-series.

## 7. REFERENCES

- 1. Kirsch, D.B., Sleep Medicine Essentials. J Clin Sleep Med. 2009; 5(4):391.
- 2. Worley SL. The Extraordinary Importance of Sleep: The Detrimental Effects of Inadequate Sleep on Health and Public Safety Drive an Explosion of Sleep Research. PT. 2018; 43(12):758-63.
- 3. Lu C, Liao B, Nie J, Wang W, Wang Y. The association between sleep duration and chronic diseases: a population-based cross-sectional study. Sleep Med. 2020;73:217-22.
- 4. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539-52.
- 5. Jiang F. Sleep and Early Brain Development. Ann Nutr Metab. 2019;75 Suppl 1:44-5.
- 6. Liu H, Chen A. Roles of sleep deprivation in cardiovascular dysfunctions. Life Sci. 2019;219:231-7.
- 7. Sleep Foundation, Sleep Stages[Internet][cited 2021 June] available from https://www.sleepfoundation.org/how-sleep-works/stages-of-sleep
- 8. Joiner WJ. The Neurobiological Basis of Sleep and Sleep Disorders. Physiology (Bethesda). 2018;33(5):317-27.
- 9. Franken P. Sleep Homeostasis. In: Binder M.D., Hirokawa N., Windhorst U. (eds) Encyclopedia of Neuroscience. Springer, Berlin, Heidelberg, 2009.
- 10. Deboer T. Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning? Neurobiol Sleep Circadian Rhythms. 2018;5:68-77.
- 11. Scholarpedia, Sleep homeostasis [Internet] [cited 2021 June ] available from http://www.scholarpedia.org/article/Sleep\_homeostasis
- 12. Rosenwasser AM, Turek FW. Neurobiology of Circadian Rhythm Regulation. Sleep Med Clin. 2015;10(4):403-12.
- 13. Sleep foundation, Circadian Rhythm [Internet] [cited 2021 June ] available from https://www.sleepfoundation.org/circadian-rhythm
- 14. Mayo clinic, Sleep disorders [Internet] [citedy 2021 June] available from https://www.mayoclinic.org/diseases-conditions/sleep-disorders/symptoms-causes/syc-20354018https://www.mayoclinic.org/diseases-conditions/sleep-disorders/symptoms-causes/syc-20354018
- 15. Rajaratnam SM, Barger LK, Lockley SW, Shea SA, Wang W, Landrigan CP et al. Health and Safety Group. Sleep disorders, health, and safety in police officers. JAMA. 2011;306(23):2567-78.

- 16. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(5 Suppl):S7-10.
- 17. K Pavlova M, Latreille V. Sleep Disorders. Am J Med. 2019;132(3):292-9.
- 18. Dopheide JA. Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. Am J Manag Care. 2020;26(4 Suppl):S76-84.
- 19. Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. Neuropsychopharmacology. 2020;45(1):74-89.
- 20. Sleep foundation, Parasomnias [Internet] [cited 2021 June ] available from https://www.sleepfoundation.org/parasomnias
- 21. Singh S, Kaur H, Singh S, Khawaja I. Parasomnias: A Comprehensive Review. *Cureus*. 2018;10(12):e3807.
- 22. Bollu PC, Goyal MK, Thakkar MM, Sahota P. Sleep Medicine: Parasomnias. Mo Med. 2018;115(2):169-75.
- 23. Mayo Clinic, REM sleep behavior disorder [Internet] [cited July 2021] available from https://www.mayoclinic.org/diseases-conditions/rem-sleep-behavior-disorder/symptoms-causes/syc-20352920
- 24. Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers*. 2018;4(1):19.
- 25. Matar E, Lewis SJ. REM sleep behaviour disorder: not just a bad dream. Med J Aust. 2017;207(6):262-8.
- 26. Ferini-Strambi L, Rinaldi F, Giora E, Marelli S, Galbiati A. REM sleep Behaviour Disorder. *Parkinsonism Relat Disord*. 2016;22 Suppl 1:S69-S72.
- 27. Slowik JM, Collen JF. Obstructive Sleep Apnea. [Updated 2020 Dec 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
- 28. Chan MTV, Wang CY, Seet E, Tam S, Lai HY, Chew EFF et al. Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators. Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery. JAMA. 2019;321(18):1788-98.
- 29. Greenstone M, Hack M. Obstructive sleep apnoea. BMJ. 2014;348:g3745.
- 30. Patel SR. Obstructive Sleep Apnea. Ann Intern Med. 2019;171(11):ITC81-ITC96.
- 31. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007;131(2):595-607.
- 32. Muza RT. Central sleep apnoea-a clinical review. J Thorac Dis. 2015;7(5):930-7.

- 33. Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician. 2008;78(2):235-40.
- 34. Guo S, Huang J, Jiang H, Han C, Li J, Xu X, Zhang G, Lin Z, Xiong N, Wang T. Restless Legs Syndrome: From Pathophysiology to Clinical Diagnosis and Management. Front Aging Neurosci. 2017;9:171.
- 35. Desautels A, Turecki G, Montplaisir J, Xiong L, Walters AS, Ehrenberg BL et al. Restless legs syndrome: confirmation of linkage to chromosome 12q, genetic heterogeneity, and evidence of complexity. Arch Neurol. 205;62(4):591-6.
- 36. National Institut of Neurologic Disorder and Stroke [Internet] [cited 2021 July] available from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Restless-Legs-Syndrome-Fact-Sheet
- 37. Sahoo D, Gosai H, Sahoo Ujjwal, Akhani P, Kanchan A, Harsoda Jaman. Mohan Assessment of daytime sleepiness and reliability test of Epworth sleepiness scale in young individuals, Tanta Medical Journal. 2014;2:79-82.
- 38. Walker NA, Sunderram J, Zhang P, Lu SE, Scharf MT. Clinical utility of the Epworth sleepiness scale. Sleep Breath. 2020;24(4):1759-65.
- 39. Doneh B. Epworth Sleepiness Scale. Occup Med (Lond). 2015;65(6):508.
- 40. Lapin BR, Bena JF, Walia HK, Moul DE. The Epworth Sleepiness Scale: Validation of One-Dimensional Factor Structure in a Large Clinical Sample. J Clin Sleep Med. 201;14(8):1293-301.
- 41. Chung F, Abdullah HR, Liao P. STOP-Bang Questionnaire: A Practical Approach to Screen for Obstructive Sleep Apnea. Chest. 2016;149(3):631-8.
- 42. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. Sleep Med Rev. 2016;25:52-73.
- 43. Asghar MS, Ahsan MN, Jawed R, Rasheed U, Ali Naqvi SA, Hassan M, Yaseen R, Mallick N, Zehra M, Saleem M. A Comparative Study on the Use of Alprazolam and Melatonin for Sleep Disturbances in Hemodialysis Patients. Cureus. 2020;12(11):e11754.
- 44. Chandrakumar D, Dorrian J, Banks S, Keage HAD, Coussens S, Gupta C, Centofanti SA, Stepien JM, Loetscher T. The relationship between alertness and spatial attention under simulated shiftwork. Sci Rep. 2020;10(1):14946.
- 45. Tan A, Yin JD, Tan LW, van Dam RM, Cheung YY, Lee CH. Using the Berlin Questionnaire to Predict Obstructive Sleep Apnea in the General Population. J Clin Sleep Med. 2017;13(3):427-32.

- 46. Killgore WD. Effects of sleep deprivation on cognition. Prog Brain Res. 2010;185:105-29.
- 47. Alhola P, Polo-Kantola P. Sleep deprivation: Impact on cognitive performance. Neuropsychiatr Dis Treat. 2007;3(5):553-67.
- 48. Karanovic N, Carev M, Kardum G, Pecotic R, Valic M, Karanovic S, Ujevic A, Dogas Z. The impact of a single 24 h working day on cognitive and psychomotor performance in staff anaesthesiologists. Eur J Anaesthesiol. 2009;26(10):825-32.
- 49. Galic T, Bozic J, Pecotic R, Ivkovic N, Valic M, Dogas Z. Improvement of Cognitive and Psychomotor Performance in Patients with Mild to Moderate Obstructive Sleep Apnea Treated with Mandibular Advancement Device: A Prospective 1-Year Study. J Clin Sleep Med. 2016;12(2):177-86.
- 50. Lusic Kalcina L, Valic M, Pecotic R, Pavlinac Dodig I, Dogas Z. Good and poor sleepers among OSA patients: sleep quality and overnight polysomnography findings. Neurol Sci. 2017;38(7):1299-306.
- 51. Pavlinac Dodig I, Krišto D, Lušić Kalcina L, Pecotić R, Valić M, Đogaš Z. The effect of age and gender on cognitive and psychomotor abilities measured by computerized series tests: a cross-sectional study. Croat Med J. 2020;61(2):82-92.
- 52. Tang, J., Liao, Y., Kelly, B. et al. Gender and Regional Differences in Sleep Quality and Insomnia: A General Population-based Study in Hunan Province of China. Sci Rep 2017:7;43690.
- 53. Amaral AP, Soares MJ, Pinto AM, et al. Sleep difficulties in college students: The role of stress, affect and cognitive processes. Psychiatry Res. 2018;260:331-7.
- 54. Becker SP, Jarrett MA, Luebbe AM, Garner AA, Burns GL, Kofler MJ. Sleep in a large, multi-university sample of college students: sleep problem prevalence, sex differences, and mental health correlates. Sleep Health. 2018;4(2):174-81.
- 55. Education Week [Internet] [cited 2021 July] available from https://www.edweek.org/leadership/homework-time/2015/11
- 56. Balart, P., Oosterveen, M. Females show more sustained performance during test-taking than males. Nat Commun 2019;10:3798.
- 57. Siedlecki KL, Falzarano F, Salthouse TA. Examining Gender Differences in Neurocognitive Functioning Across Adulthood. J Int Neuropsychol Soc. 2019;25(10):1051-60.
- 58. Ardila A, Rosselli M, Matute E, Inozemtseva O. Gender differences in cognitive development. Dev Psychol. 2011;47(4):984-90.
- 59. Jäncke L. Sex/gender differences in cognition, neurophysiology, and neuroanatomy. F1000Res. 2018;7:F1000.

## 8. SUMMARY

**Objectives:** The aim of this study was to compare cognitive and psychomotor performance between men and women and to compare daytime sleepiness assessed with the Epworth sleepiness scale (ESS) and Stanford sleepiness scale (SSS), subjective sleep quality assessed with Pittsburgh sleep quality index (PSQI) and sleep habits between men and women. Furthermore, we investigated the association between cognitive and psychomotor performance on three tests of the computer based system Complex Reactionmeter Drenovac (CRD-series), and daytime sleepiness assessed and subjective sleep.

**Patients and methods:** A total of 168 medical students from the University of Split School of Medicine were included in the research: 49 men with a median age of 20, ranging from 19 to 25, and 119 women with a median age of 21, ranging from 19 to 23. All students filled in the SSS, ESS, PSQI and sleep habits questionnaire. Afterwards the students performed three tests on the CRD-series battery (CRD11, CRD311, CRD411).

**Results:** In the PSQI there was a statistically significant higher score in women  $(5.68\pm2.53)$  compared to men  $(4.80\pm2.14, P=0.023)$ . The SSS score was also significantly higher in women in contrast to men  $(2.82\pm1.22 \text{ vs. } 2.23\pm0.98, \text{ respectively, } P=0.002)$ . Women also stated to sleep shorter  $(6h35\text{min} \pm 1h 8\text{min})$  than men  $(6h 58\text{min} \pm 58 \text{ min, } P=0.024)$ . Chronic tiredness was significantly more frequent among women than men (P=0.007). On the CRD11 test men had statistically significant shorter MinT and TTST (TTST  $94.46\pm14.84 \text{ s}$  and MinT  $1.61\pm0.23 \text{ s}$ ) than women (TTST  $105.82\pm17.78 \text{ s}$  and MinT  $1.78\pm0.28 \text{ s}$ , P<0.001 for both comparisons). In the CRD411 men were also significantly faster than women (TTST  $26.94\pm4.76 \text{ s}$  vs.  $31.22\pm7.12 \text{ s}$  for TTST and  $0.30\pm0.07 \text{ vs. } 0.43\pm0.08 \text{ s}$  for MinT, respectively, P<0.001 for both comparisons). On the CRD311 test women needed significantly more time to complete the whole test than men (TTST was  $28.18\pm2.46 \text{ s}$  in women and  $27.43\pm2.09 \text{ s}$  in men, P=0.047). No significant correlation was found between the performance on CRD series test and sleepiness, assessed with the ESS and SSS, sleep quality assessed with PSQI and subjective sleep duration.

Conclusion: Our results showed that men had shorter reaction times than women on three tests (CRD11, CRD311 and CRD411) of the CRD-series, while women had shorter sleep duration and worse sleep quality assessed with PSQI than men and experienced more daytime sleepiness assessed with SSS but there was no difference in daytime sleepiness assessed with ESS between men and women. We found no correlation between daytime sleepiness and performance on the tests of the CRD-series and between sleep quality and performance on the tests of the CRD-series.

9. CROATIAN SUMMARY

**Naslov:** Povezanost između samoprocjene spavanja te kognitivnog i psihomotoričkog učinka u studenata medicine

Ciljevi: Cilj ovog istraživanja bio je usporediti kognitivne i psihomotoričke učinke muškaraca i žena te usporediti dnevnu pospanost procijenjenu s Epworthovom ljestvicom pospanosti (ESS) i Stanfordskom ljestvicom pospanosti (SSS), subjektivnu kvalitetu spavanja procijenjenu Pittsburgh upitnikom kvalitete spavanja (PSQI) i navike spavanja između muškaraca i žena. Nadalje, istražit ćemo povezanost kognitivnih i psihomotoričkih učinaka na tri testa sustava Complex Reactionmeter Drenovac (CRD-serija), te dnevne pospanosti i subjektivne kvalitete spavanja.

**Pacijenti i metode:** U istraživanje je bilo uključeno ukupno 168 studenata medicine iz Medicinskog fakulteta Sveučilišta u Splitu i to 49 muškaraca sa srednjom dobi od 20 (raspon 19-25) i 119 žena srednje dobi od 21 (raspon 19-23) godina. Svi su studenti popunili SSS, ESS, PSQI i upitnik o navikama spavanja. Nakon toga studenti su riješili tri testa na CRD seriji (CRD11, CRD311, CRD411).

**Rezultati:** U PSQI zabilježen je viši rezultat u žena  $(5,68\pm2,53)$  nego u muškaraca  $(4,80\pm2,14, P=0,023)$ . SSS rezultat je također bio značajno viši u žena za razliku od muškaraca  $(2,82\pm1,22)$  naspram  $2,23\pm0,98$ , odnosno P=0,002). Žene su također izjavile da spavaju kraće  $(6h35min\pm1h8min)$  od muškaraca  $(6h58min\pm58min, P=0,024)$ . Kronični umor bio je značajno češći u žena nego u muškaraca (P=0,007). Na CRD11 testu muškarci su imali značajno kraće MinT i TTST  $(TTST\ 94,46\pm14,84\ s\ i\ MinT\ 1,61\pm0,23\ s)$  od žena  $(TTST\ 105,82\pm17,78\ s\ i\ MinT\ 1,78\pm0,28\ s, P<0,001\ za\ obje usporedbe)$ . Na CRD411 muškarci su također bili značajno brži od žena  $(TTST\ 26,94\pm4,76\ s\ nasuprot\ 31,22\pm7,12\ s\ za\ TTST\ i\ 0,30\pm0,07\ s\ naspram\ 0,43\pm0,08\ s\ za\ MinT,\ odnosno\ P<0,001\ za\ obje usporedbe)$ . Na CRD311 testu ženama je trebalo više vremena da ispune cijeli test nego muškarcima  $(TTST\ je\ bio\ 28,18\pm2,46\ s\ u\ žena\ i\ 27,43\pm2,09\ s\ u\ muškaraca, <math>P=0,047$ ).

Nije pronađena značajna korelacija između učinka na testu CRD serije i pospanosti, procijenjene ESS i SSS te kvalitete spavanja procijenjene PSQI i subjektivnog trajanja spavanja.

**Zaključak:** Naši su rezultati pokazali da su muškarci imali kraća vremena reakcije od žena na tri testa (CRD11, CRD311 i CRD411) CRD serije, dok su žene imale kraće trajanje sna i lošiju kvalitetu spavanja procijenjenu PSQI upitnikom od muškaraca te su imale veću dnevnu pospanost procijenjenu SSS-om, ali nije bilo razlike u dnevnoj pospanosti procjenjenoj ESS-om između muškaraca i žena. Nismo pronašli korelaciju između dnevne pospanosti i učinka na testovima CRD serije te između kvalitete spavanja i učinka na testovima serije CRD.

# 10. CURRICULUM VITAE

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