Attention please: vigilance in patients with excessive daytime sleepiness

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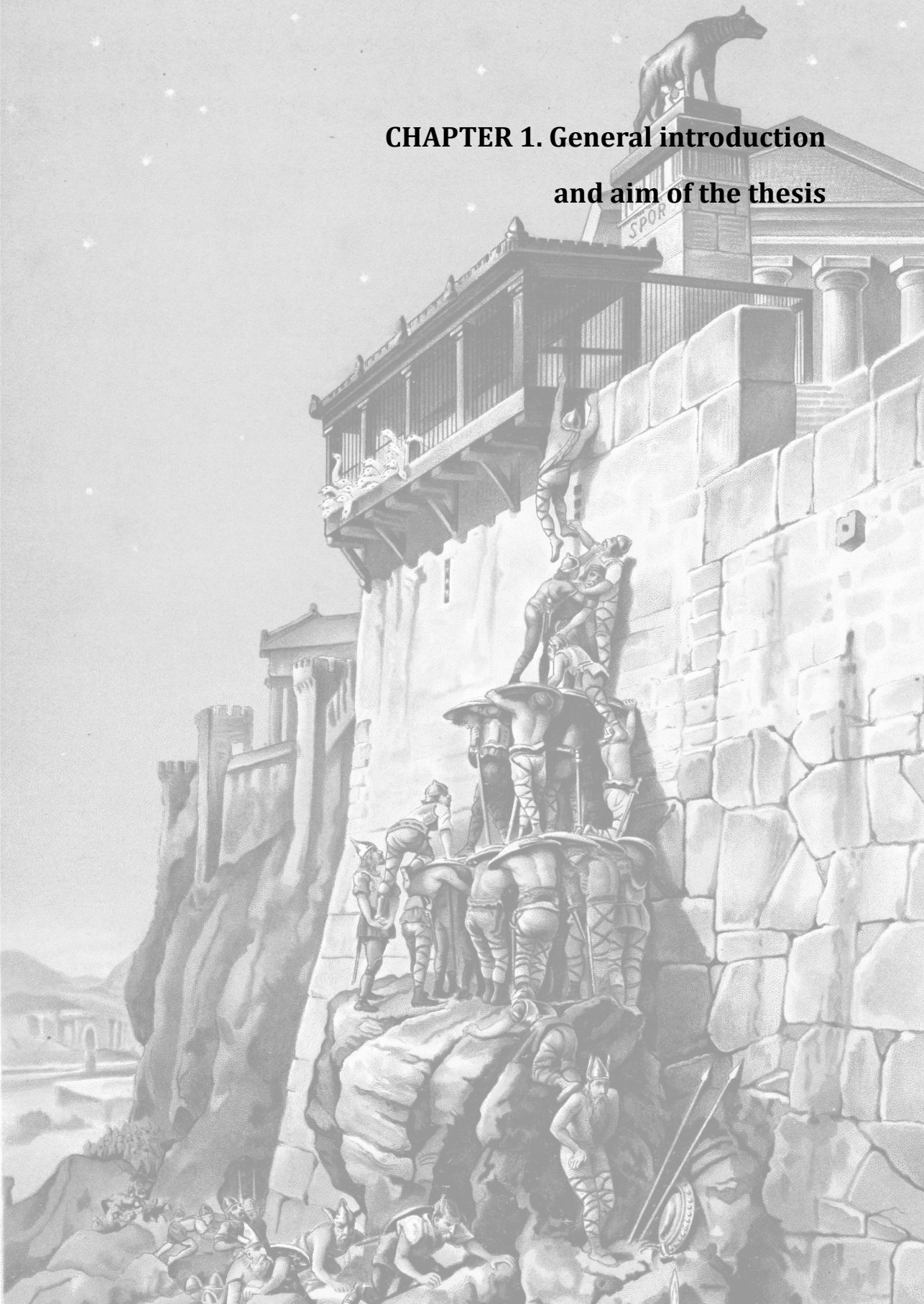


CHAPTER 1. General introduction and aim of the thesis

Sleep disorders

Various healthcare professionals are active in the field of sleep medicine: neurologists, pulmonologists, otolaryngologists, dentists, general practitioners and psychologists, all of whom participate in the diagnosis or treatment of sleep disorders. Neurologists are mostly involved in disorders with excessive daytime sleepiness (also referred to as central disorders of hypersomnolence)[1], a disturbed 24-hour sleep-wake cycle (circadian rhythm disorders), and disorders with abnormal behaviour during sleep (so-called parasomnias, e.g. sleep walking, night terror, REM-sleep behaviour disorder). This thesis focuses on disorders characterised by excessive daytime sleepiness.

Disturbed vigilance in excessive daytime sleepiness

Arriving at the diagnosis of a sleep disorders starts with a careful history, which in many cases leads to, if not the diagnosis, a strong suspicion. In this respect much attention has bene given to one symptom, excessive daytime sleepiness (EDS). As this is essentially a subjective phenomenon, it is not surprising that sleep questionnaires constitute a major approach to quantify its severity. One such, the Epworth Sleepiness Scale (ESS)[2], became widely accepted as an important test in the 1990s. The ESS asks respondents to judge the likelihood of falling asleep in certain circumstances, such as 'after lunch', 'in the car when waiting for the traffic light for 5 minutes' or 'when conversing with someone'. Apart from the questionnaire approach, other tests aimed to quantify EDS by measuring physiological variables: the 'Multiple Sleep Latency Test' (MSLT)[3] requires patients to actually fall asleep when given the opportunity to do so, and measures how long it takes patients to do so (MSLT, box 1). The 'Maintenance of Wakefulness Test' (MWT, box 2)[4] measures the ability to resist sleepiness, and also measures the time it takes to fall asleep, but now when patients are asked to not do so. Whether these latter tests assess the same matter as the EDS questionnaires is not a given, and will be discussed below.

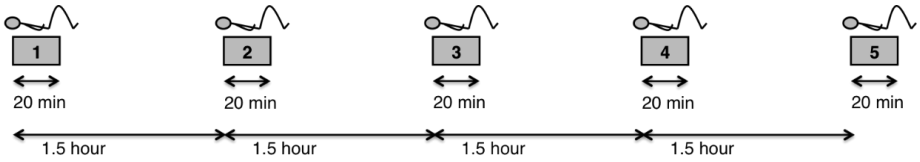
This focus on sleepiness has somewhat overshadowed other important problems that patients with sleep disorders may experience.

Box 1 – Multiple Sleep Latency Test

The MSLT asks subjects to fall asleep in a quiet and dimmed room multiple times on one day. A standardised MSLT consists of four to five twenty-minute sessions with one and a half to two-hour intervals. The subject is asked to stay in bed for the whole session, even when no sleep occurs. Electroencephalograpy for standard sleep recording is performed. Sleep onset is defined as the first 30-second epoch of any sleep stage, including stage I. The primary outcome measure is the average of all four to five sleep-onset latencies obtained

from the separate test sessions over the day. When no sleep occurs, sleep latency is noted as 20 minutes. A secondary outcome measure is the occurrence of sleep-onset rapid eye movement episodes.

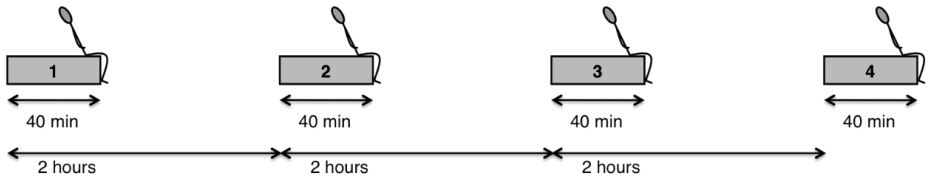
In the studies described in this thesis an MSLT consists of a five-session protocol.



The MSLT was introduced in 1977[5], standardised and accepted in 1986[3]. Test-retest reliability, inter- and intra-rater reliability were all high in a small group of healthy individuals.[6-8] The construct validity of the MSLT to measure sleepiness was based on application of the test to a group of healthy individuals who were sleep deprived[9]. The severity of deprivation during one night proved to be significantly correlated to sleep latency the next day. This suggested that sleep latency, as assessed with an MSLT, indeed represented an objective quantitative marker of sleepiness, at least after sleep deprivation in healthy subjects. The concept was consolidated by the finding that sedative drugs decreased sleep latency[10], and by the finding that the sleep latencies proved abnormally short in patients with narcolepsy and obstructive sleep apnoea[11-13]. No studies were performed to obtain normative data in large population-based cohorts.

Box 2 – Maintenance of Wakefulness Test

The MWT is similar to the MSLT except for one major difference: subjects are instructed to sit still and remain awake while seated in bed in a quiet and dimly-lit room, based on the concept that this task represents the difficulties of daily life of patients with EDS better than their ability to fall asleep. No excessive movement or talking to prevent sleep is allowed. The MWT consists of four 40-minute sessions performed at two-hour intervals. Sleep onset is defined as the first 30-second epoch of any sleep stage, including stage I[14]. Sessions are terminated after 40 minutes if no sleep occurs, or after sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep. A technician has to be present to score sleep continuously. The primary outcome measure is the mean sleep latency (the arithmetic mean of the four sessions).



The MWT was developed in 1982 after it turned out that the MSLT disappointed as a tool to measure treatment efficacy.[4] Although patients felt a subjective improvement after treatment, felt more alert and were better able to stay awake, this was not reflected by the MSLT. Their sleep latency remained short.[15] The MWT proved to detect treatment effects better than the MSLT. However, the correlation with subjective improvement and performance was still only moderate, with the exception of driving performance in obstructive sleep apnoea patients.[16]

One such problem is impaired vigilance. Awake people should become aware of changes in their environment, so they can respond to these changes, if necessary. This capability is called 'vigilance'. Vigilance is a fundamental prerequisite for higher cognitive functions required in daily life, for instance at school or work. Subtle disturbances of vigilance are common in daily life, causing cognitive mishaps, such as forgetting why you went up the stairs, or reading a piece of text more than once without registering the content.

Since vigilance refers to a capability to be aware of internal or external stimuli, wakefulness is a prerequisite for vigilance. When people are asleep or falling asleep, they will not be able to become aware of stimuli either. This state is easily confused with a disturbed vigilance, as the results are the same in that the detection of stimuli is diminished. Caution is warranted to prevent confusing sleepiness with a vigilance disturbance. Vigilance refers to a quality of the awake state only; no inferences can be made about vigilance in people who are not awake.

Type 1 narcolepsy

An excellent example of a condition with severely disturbed vigilance is the primary sleep disorder narcolepsy, type 1.[1] The disorder is caused by loss of hypocretin-producing neurons in the lateral hypothalamus. Type 1 narcolepsy is characterised by severe EDS and cataplexy. The presence of chronic EDS, i.e. daily episodes of an irrepressible need to sleep or daytime lapses into sleep, is mandatory for the diagnosis of narcolepsy. The presence of cataplexy, a sudden partial or complete drop of muscle tone with preserved consciousness triggered by certain emotions, is a prerequisite to diagnose type 1 narcolepsy, but has to be absent in type 2. Additional symptoms of either type include disturbed nocturnal sleep, as well as a range of signs and symptoms that are pathophysiological associated with rapid eye movement (REM) sleep. These are

hypnagogic hallucinations and sleep paralysis.[17] A disturbed vigilance is an additional, largely neglected, symptom of narcolepsy. Note that this does not refer to a consequence of being or falling asleep, but to an aspect of being awake. A disturbed vigilance is directly related to impaired daytime performance and quality of life.[18,19] Examples of the severe vigilance problems experienced by patients with narcolepsy are difficulty in recalling the content of a conversation, finishing a book, or concentrating on studies or work.

Vigilance problems can have life-threatening consequences, e.g. when driving a car or working with potentially dangerous machines under such circumstances. As the consequences of vigilance impairment can be serious, vigilance impairments need to be quantified; something not reflected by the abovementioned questionnaire, nor by the MSLT or MWT.

These currently used sleep tests have other shortcomings. Although the MSLT in particular has contributed to a more precise classification system of sleep disorders, several percent of the normal population may show abnormal test results and therefore fulfil criteria for 'hypersomnia', even though they have no corresponding complaints at all.[20] The MSLT should therefore always be interpreted in the context of a patient's specific symptoms and other test results. As mentioned above, the MSLT is not sensitive to EDS treatment effects, showing it misses important aspects of sleepiness. The MWT and sleep questionnaires have been shown to be more sensitive to detect improvement in pharmacological trials than the MSLT. The MWT is also used in the assessment of safety issues, such as the inability to remain awake during driving. However, there is little evidence of any link between the mean sleep latency as assessed by the MWT and the accident risk in real world circumstances. Moreover, the MWT and sleep questionnaires do not reflect functional improvements during the awake state; while patients reported to be more alert when awake, the sleep latency tests remained unaltered.[14]

Measuring vigilance in sleep disorders

Quantifying how the activities of daily life are impaired by sleep disorders, or how treatment ameliorates such functions, proves to be remarkably difficult. A possible solution is to quantify vigilance itself, since it is a prerequisite for cognitive functions. Descriptions of vigilance measurements in disorders of EDS are limited to a few publications on patients with narcolepsy (see also box 1)[19] and to some contrasting publications on patients with obstructive sleep apnoea syndrome, a sleep-related breathing disorder.[21-25]

Several methods have been proposed to measure vigilance. Examples include subjective visual-analog scales, pupillography [26], quantified electro-encephalography (EEG) [27], brain imaging[28], and a variety of response tasks assessing sustained attention. An ideal test would provide an objective quantification of the level of vigilance while being easy and cheap to administer. These practical requirements are best met by response tasks assessing sustained attention. A conceptual advantage of such tests is that

they also assess the response to a stimulus. In other words, these tests are not limited to the recording of a derivate of brain activity, but are extended to quantify the patient's capability to act upon a trigger. One such test is the Sustained Attention to Response Task (SART) [29], a 4-minute 19-second computer task in which subjects should withhold presses to one out of nine stimuli (box 3).[29,30] This test has been demonstrated capable of quantifying vigilance impairment in narcolepsy patients.[19]

Box 3 - The Sustained Attention to Response Task (SART)

The SART is a go/no-go task in which the no-go target appears unpredictably and rarely, and in which both accuracy and response speed, quantified as reaction time, are important. It lasts 4 minutes and 19 seconds and comprises the numbers 1–9 appearing 225 times in random order and in different sizes in a white font on a black computer screen. Subjects have to respond to the appearance of each number by pressing a button while seated in a dimly-lit room, except when the number is a 3, which occurs 25 times in all. Subjects have to press the button before the next number appears, and are instructed to give equal importance to accuracy and speed in performing the task.[29,30] The primary outcome measure of the SART is the total error score, consisting of, firstly, key presses when no key should be pressed (i.e. after a '3', a so-called 'no-go trial': commission errors), and secondly absent presses when a key should have been pressed (i.e. after anything but a '3', the so-called 'go trials': omission errors).

The SART was initially developed to investigate lapses of sustained attention in individuals with traumatic brain injury[29,30], but appeared to be a promising test in patients with type 1 narcolepsy.[19]

Scope of the present thesis

This thesis covers several steps in the process of validating the SART as a measure of vigilance in patients with excessive daytime sleepiness.

Part I - Measuring vigilance with the SART

Although functional impairments as a result of insufficient vigilance have gradually become recognized in patients with EDS, measurements of vigilance are still scarce. A scrutiny of such publications shows that definitions of 'vigilance' differ between publications. Chapter 2 deals with these different definitions, and proposes a new definition of vigilance. Chapter 3 extends previous vigilance measurements in narcolepsy

through application of the SART to include other patient groups with excessive daytime sleepiness. Chapter 4 analyses various factors possibly influencing SART outcome measures, such as task repetition, napping, time of day, and test instruction.

Part II – The SART as a treatment effect parameter in EDS

The chapters in this part deal with the SART as a tool to measure treatment efficacy in sleep studies. Chapters 5 and 6 describe SART results in narcolepsy patients before and after treatment. Chapter 5 contains a comparison of the SART, ESS and MWT before and after treatment with modafinil, pitolisant or placebo. In Chapter 6, the SART is compared to the Psychomotor Vigilance Test (PVT; see Box 4)[31-33], MWT, and Oxford Sleep Resistance test (OSLER; see Box 4)[34] before and during treatment with sodium oxybate. Chapter 7 deals with the SART to assess continuous positive airway pressure in obstructive sleep apnoea.

Box 4 – Other measurements of vigilance and sleepiness

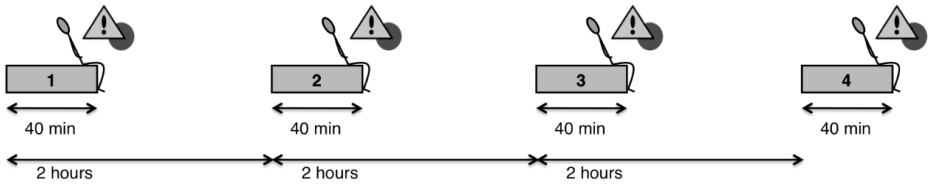
The Psychomotor Vigilance Test (PVT)

The PVT is a reaction time task. Subjects are instructed to press a button as quickly as possible to stop a digital millisecond counter as soon as it starts running, which it does at variable intervals (interstimulus intervals: 2-10 seconds). The task requires continuous attention to detect the randomly occurring stimuli. PVT tests of various durations are available; the best-validated test duration lasts 10 minutes. Outcome measures vary between studies. Frequently used measures are the frequency of lapses, defined as the number of times the subject fails to respond within 500 ms or fails to respond at all; the average reaction time; the average of the 10% longest or shortest reaction times per session. The PVT is widely applied in sleep-deprivation studies.[31-33,35] Only recently some normative data in sleep disorders have become available.[36]

The Oxford Sleep Resistance test (OSLER)

The OSLER is a behavioural version of the MWT. It follows the same schedule and subjects are similarly positioned. Instead of electroencephalographic recording of sleep onset, subjects are required to respond to a non-arousing visual stimulus. The subject's index finger is placed on a sensor. A red light is positioned four to

six feet away at eye level in the frontal visual field. The light flashes regularly for 1 second every 3 seconds. Subjects are instructed to lift their finger from the sensor for 1 second when the red light flashes. Sleep onset is defined as seven consecutive omissions, i.e. non-responding to flashes for ≥ 18 seconds. Similar to the MWT, a session is terminated when sleep onset occurs or after 40 minutes of being awake. The primary outcome measure is the mean of the four sleep onset latencies. The OSLER has the advantage of not requiring constant presence of a technician.



The OSLER has been validated in patients with obstructive sleep apnoea.[34]

REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders. Diagnostic and Coding Manual.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540-545.
3. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep.* 1986;9(4):519-524.
4. Mitler MM, Gujavarty KS, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol.* 1982;53(6):658-661.
5. Carskadon MA, Dement WC. Sleep tendency: an objective measure of sleep loss. *Sleep Res.* 1977;6:200.
6. Zwyghuizen-Doorenbos A, Roehrs T, Schaefer M, Roth T. Test-retest reliability of the MSLT. *Sleep.* 1988;11(6):562-565.
7. Drake CL, Rice MF, Roehrs TA, Rosenthal L, Guido P, Roth T. Scoring reliability of the multiple sleep latency test in a clinical population. *Sleep.* 2000;23(7):911-913.
8. Benbadis SR, Qu Y, Perry MC, Dinner DS, Warnes H. Interrater reliability of the multiple sleep latency test. *Electroencephalogr Clin Neurophysiol.* 1995;95(4):302-304.
9. Carskadon MA, Dement WC. Effects of total sleep loss on sleep tendency. *Perceptual and motor skills.* 1979;48(2):495-506.
10. Bliwise D, Seidel W, Karacan I, et al. Daytime sleepiness as a criterion in hypnotic medication trials: comparison of triazolam and flurazepam. *Sleep.* 1983;6(2):156-163.
11. Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr Clin Neurophysiol.* 1978;45(5):621-627.
12. Mitler MM, Van den Hoed J, Carskadon MA, et al. REM sleep episodes during the Multple Sleep Latency Test in narcoleptic patients. *Electroencephalogr Clin Neurophysiol.* 1979;46(4):479-481.
13. Dement W, Carskadon MA, Richardson G. *Excessive daytime sleepiness in the sleep apnea syndrome.* New York: Alan R Liss; 1978.
14. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep.* 2005;28(1):113-121.

15. Roth T, Hartse KM, Zorick F, Conway W. Multiple naps and the evaluation of daytime sleepiness in patients with upper airway sleep apnea. *Sleep.* 1980;3(3-4):425-439.
16. Philip P, Sagaspe P, Taillard J, et al. Maintenance of Wakefulness Test, obstructive sleep apnea syndrome, and driving risk. *Ann Neurol.* 2008;64(4):410-416.
17. Scammell TE. Narcolepsy. *The New England journal of medicine.* 2015;373(27):2654-2662.
18. Valley V, Broughton R. Daytime performance deficits and physiological vigilance in untreated patients with narcolepsy-cataplexy compared to controls. *Review of electroencephalograpy and clinical neurophysiology.* 1981;11(1):133-139.
19. Fronczek R, Middelkoop HA, van Dijk JG, Lammers GJ. Focusing on vigilance instead of sleepiness in the assessment of narcolepsy: high sensitivity of the Sustained Attention to Response Task (SART). *Sleep.* 2006;29(2):187-191.
20. Mignot E, Lin L, Finn L, et al. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. *Brain.* 2006;129(Pt 6):1609-1623.
21. K G, AA B, JF G, et al. - Cognitive impairment in obstructive sleep apnea. *D - 0265365.* (- 1768-3114 (Electronic)):- 233-240.
22. L F-S, C B, MR DG, et al. - Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial. *D - 7605818.* (- 0361-9230 (Print)):- 87-92.
23. SF Q, CS C, WC D, et al. - The association between obstructive sleep apnea and neurocognitive. *D - 7809084.* (- 1550-9109 (Electronic)):- 303-314B.
24. Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd DG, Suratt PM. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. *Chest.* 1986;90(5):686-690.
25. Findley L, Unverzagt M, Guchu R, Fabrizio M, Buckner J, Suratt P. Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. *Chest.* 1995;108(3):619-624.
26. Morad Y, Lemberg H, Yofe N, Dagan Y. Pupillography as an objective indicator of fatigue. *Current eye research.* 2000;21(1):535-542.
27. Coenen AM. Neuronal activities underlying the electroencephalogram and evoked potentials of sleeping and waking: implications for information processing. *Neuroscience and biobehavioral reviews.* 1995;19(3):447-463.
28. Olbrich S, Mulert C, Karch S, et al. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. *Neuroimage.* 2009;45(2):319-332.
29. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia.* 1997;35(6):747-758.
30. Manly T, Robertson IH, Galloway M, Hawkins K. The absent mind: further investigations of sustained attention to response. *Neuropsychologia.* 1999;37(6):661-670.
31. Dinges DF, Kribbs NB. Performing while sleepy: effects of experimentally-induced

sleepiness In: Monk TH, ed. *Sleep, sleepiness & Performance.* Chister, UK: Wiley; 1991:97-128.

32. Dinges DF, Powell JW. Sleepiness is more than lapsing. *Sleep Res.* 1988;17(84).
33. Dorrian J, Rogers NL, Dinges DF. Psychomotor vigilance performance: a neurocognitive assay sensitive to sleep loss. In: Kushida C, ed. *Sleep deprivation: Clinial Issues, Pharmacology and Sleep Loss Effects.* New York: Marcel Dekker; 2005:39-70.
34. Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. *J Sleep Res.* 1997;6(2):142-145.
35. Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep.* 2011;34(5):581-591.
36. Thomann J, Baumann CR, Landolt HP, Werth E. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. *J Clin Sleep Med.* 2014;10(9):1019-1024.