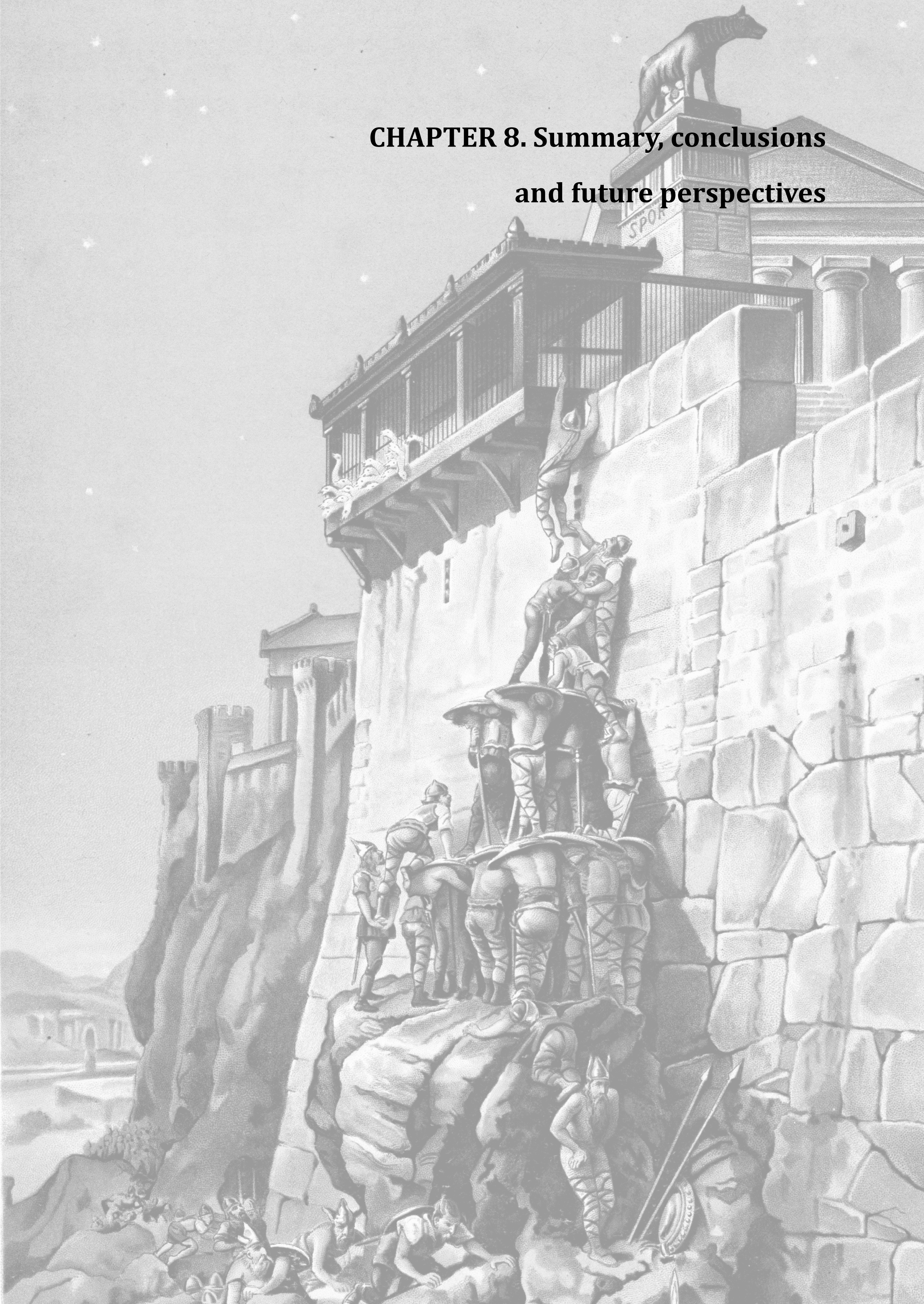
Attention please: vigilance in patients with excessive daytime sleepiness

Schie, M.K.M. van

CHAPTER 8. Summary, conclusions and future perspectives



GENERAL INTRODUCTION AND AIM OF THE THESIS

Patients with sleep disorders often experience problems in daily life due to impaired vigilance. Type 1 narcolepsy, a disorder caused by hypocretin deficiency, is an excellent example of a disorder of severely disturbed vigilance. Chapter 1 offered an introduction to the measurement of vigilance impairment in sleep disorders. While several methods have been proposed to measure vigilance impairment, only few have been applied to sleep disorders and none have explicitly been validated in these patient groups. Promising results have been observed in a study of Sustained Attention to Response Task (SART) measurements in patients with type 1 narcolepsy.[1] The SART is a 4-minute 19-second lasting go-/no-go task assessing sustained attention.[2,3] This thesis covers several steps in the validation process of the SART as a means to quantify vigilance in sleep disorders.

PART I – MEASURING VIGILANCE

This part addresses basic aspects of vigilance measurements in sleep disorders. Chapter 2 deals with different definitions of vigilance with the aims of discussing the various concepts involved and arriving at a new definition. Chapter 3 extends previous vigilance measurements in narcolepsy by means of the SART to include other sleep disorders than narcolepsy. Various aspects possibly influencing SART outcome are analysed in Chapter 4, such as task repetition, napping, time of day, and test instruction. These chapters will now be discussed separately and briefly.

Challenges in defining vigilance

Chapter 2 addresses the differences between variously proposed definitions of the concept ‘vigilance’. All the identified variants of the definition of vigilance proved to be linked to aspects of alertness, sustained attention and arousal; in turn, all these concepts were themselves the subject of variable interpretations. We proposed a new definition of vigilance; it is defined as the capability to be aware of potential changes in one’s environment, including a quantitative dimension, expressed as a level of alertness, and a temporal dimension. Attention adds a goal-directed focus to this capability. Sustained attention refers to prolongation of this capability over time. To disentangle the various related concepts, we found it necessary to also specify what we mean by arousal. To do so we upheld its linguistic meaning, so we define arousal as an upward change in alertness taking place in a short time.

Vigilance is defined as the capability to be aware of potential changes in one's environment, including a quantitative and a temporal dimension.

Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness.

Chapter 3 described a cross-sectional study of the SART as a tool to measure vigilance in patients with different causes of excessive daytime sleepiness: 42 patients with type 1 narcolepsy, 5 with type 2 narcolepsy, 37 with idiopathic hypersomnia, and 12 with obstructive sleep apnoea syndrome (OSAS). The main finding was that the SART error rate was high in all four patient groups. The median SART error count did not differ between groups, nor did other SART descriptors. This result confirmed the previous suggestion that a high SART error count was not specific for any disease entity. Instead, a high error count probably reflects a key symptom of the disorders in question, i.e. a vigilance impairment. The previously reported absence of a correlation between the SART error count and sleep latency in the multiple sleep latency task (MSLT) already implied that vigilance and sleepiness represent different phenomena.[1] The SART error count proved inversely correlated with reaction time variability, and the number of commission errors was inversely correlated with mean reaction time. These relations have previously been explained as the so-called 'speed–accuracy trade-off'.[2-5] We found diurnal effects on SART performance, with the highest SART error count at the first session in the morning. This higher error score may reflect a brief learning period or an underlying time-of-day effect.

Vigilance, as quantified by the SART, is as impaired in type 1 narcolepsy as it is in other causes of excessive daytime sleepiness. The absence of a correlation between SART and MSLT measurements indicates that the two tests measure separate constructs.

The influences of task repetition, napping, time of day, and instruction on the Sustained Attention to Response Task

Chapter 4 dealt with the possible influences of time of day, napping, repetition, and instruction on the performance on two consecutive sessions of the SART in 100 healthy subjects. The aim was to unravel the mechanism responsible for a decrease in SART error count from the first to the second SART session (See also Chapter 3). The first part of the study comprised a 2x2 design with two time-of-day groups (morning or afternoon) and two nap groups (20-minute nap one hour before the second SART session versus no nap) in 80 healthy subjects. Twenty additional subjects took part in the second study part, to provide a match for 20 subjects from the first study part; they followed the same procedure, but with a different test instruction.

The results demonstrated that an improvement from the first to the second SART session was only found when subjects were instructed to pay attention to accuracy and to ignore response speed. The improvement is likely attributed to an effect of repetition, i.e. a learning effect, although subjects were not aware of such an effect, given their own performance judgments. This repetition effect was sufficiently minimized after a full 4-minute 19-second practice session. The effect of the specific instruction given probably also explains why some previous studies reported a learning effect[1], in contrast to other studies.[6]

This study also demonstrated that the SART error count was significantly higher in healthy subjects who were instructed to pay equal attention to accuracy and speed than in those instructed to pay attention to accuracy only and to ignore response speed. The 'accuracy first' instruction led to a lower error count with lower between-subject variability. As such, it is the preferred instruction to use when it is importance to assess the best error count. The 'accuracy first' instruction also yielded the largest difference in error score between narcolepsy patients and controls.

In addition, this study also showed that a nap opportunity of 20 minutes more than one hour prior to a SART session did not influence the error count of that session in healthy subjects. The time of day had no clear effect on the SART error count; if such an effect existed at all, it was small and occurred only following the instruction to pay equal attention to accuracy and speed. The 'accuracy first' instruction allowed a comparison between SART sessions administered at different times of the day during normal working hours.

The 'accuracy first' instruction is best suited to assess the lowest error count a subject can achieve. To minimize the consequences of the learning effect that has been observed when using this instruction, we strongly recommend the use a full 4-minute 19-second practice session. Time of day during regular working hours and a nap occasion, as is present in the MSLT, do not influence SART results in healthy controls.

PART II - SUSTAINED ATTENTION TO RESPONSE TASK AS A TREATMENT-EFFECT PARAMETER IN DISORDERS CHARACTERISED BY EXCESSIVE DAYTIME SLEEPINESS

The chapters in this part dealt with the SART as a parameter of treatment efficacy in sleep studies. Chapters 5 and 6 concern measurements in type 1-narcolepsy patients. These chapters differ in two ways: the treatment that was investigated (pitolisant versus sodium oxybate) and the other outcome measurements in addition to the SART (ESS and MWT versus PVT, OSLER and MWT). Chapter 7 comprises the SART as a parameter of treatment efficacy parameter of continuous positive airway pressure in obstructive sleep apnoea.

Comparing treatment effect measurements in narcolepsy: the SART, ESS and MWT

Chapter 5 described the validation of the SART as a parameter of treatment efficacy in narcolepsy, comparing its performance to that of the Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS). This study was performed within a randomized controlled, double-blind, parallel-group, multicentre trial comparing the effects of 8-week treatments with pitolisant, modafinil, or placebo in ninety-five patients with type 1 or 2 narcolepsy.[7] MWT, ESS, and SART were administered at baseline and after an 8-week treatment period. The severity of excessive daytime sleepiness and cataplexy was also assessed using the Clinical Global Impression scale (CGI-C). Both reliability and sensitivity of SART, MWT and ESS as compared to the CGI-C were addressed. The SART, MWT, and ESS all had good reliability, obtained for the SART and MWT using two to three sessions in one day. The log-transformed SART commission error count proved the most reliable SART parameter across sessions performed on the same day; a good reliability, of > 0.8, was already reached after two SART sessions. Performing the SART three times allowed the log-transformed total error count to exceed this threshold.

The ability to distinguish responders from non-responders, classified using the CGI-C score, was high for all measures, with a high performance for the log-transformed total error count ($r = 0.61$) and the ESS ($r = 0.54$). A subsequent factor analysis indicated that changes in MWT and ESS during the study largely reflected the same aspect of the narcolepsy burden, whereas the SART reflected a completely different aspect. The factor analysis showed that the investigator’s impression is both based on sustained attention and the ability to stay awake.

This study showed that the SART, in particular the number of commission errors and the total error score, is a valid measure to detect treatment effects in type 1 narcolepsy. A combination of the SART and ESS provides a comprehensive evaluation of treatment effects: while the ESS represents a subjective estimate of how sleepy patients feel, the SART is objective in nature. Together they share the advantages of requiring little time and money and correlating well with the clinical global assessment of patient improvement.

Improved vigilance after sodium oxybate treatment in narcolepsy

Chapter 6 reports a two-centre observational study of vigilance measurements in 26 patients with type 1 narcolepsy and 15 healthy controls. The aim of this study was to assess the feasibility of vigilance measurements on multiple days using the SART and the Psychomotor Vigilance Test (PVT) with portable equipment, and subsequently to assess the effect of sodium oxybate treatment on vigilance in narcolepsy patients. The study concerned two measurement of the MWT and Oxford Sleep Resistance test (OSLER), followed by seven-day portable vigilance battery measurements. This procedure was repeated for narcolepsy patients after at least three months of stable treatment with sodium oxybate. Ambulatory administration of SART and PVT proved feasible in both narcolepsy patients and controls. These, as well as OSLER and MWT measurements, revealed worse performance by narcolepsy patients compared to controls. Sodium oxybate treatment was associated with a better resistance to sleep measured by the MWT. Moreover, treatment was associated with a small improvement in sustained attention, quantified by both OSLER and SART but not PVT.

Portable measurements of sustained attention as well as in-laboratory OSLER and MWT measurements revealed worse performance for narcolepsy patients compared to controls. Sodium oxybate treatment was associated with an improvement of sustained attention and a better resistance to sleep. The SART and OSLER offer solutions for a less time- and manpower-consuming evaluation of treatment effects in patients with narcolepsy than PVT and MWT.

Predictors of patient-rated improvement on continuous positive airway pressure for obstructive sleep apnea syndrome

Chapter 7 describes a prospective observational treatment-efficacy study of continuous positive airway pressure (CPAP) in OSAS. The study aimed at investigating which parameters best predicted patient-rated improvement. Candidate parameters included breathing indices (the apnoea-hypopnoea index -AHI), questionnaires of sleepiness (ESS and the Stanford Sleepiness Scale), the SART, and visual-analogue scales of several aspects of well-being. Improvement was scored using the patient-rated Clinical Global Impression of Change (PCGI-C). Thirty OSAS patients with an AHI >15 were investigated during two pre-treatment visits and one visit after 8 weeks of CPAP. A marked improvement after CPAP was observed for all breathing parameters, as well as the ESS, whereas only marginal improvements were observed for SART performance and some visual-analogue scales. Eighty percent of patients considered themselves improved on the PCGI-C. This improvement correlated well with improvement of breathing parameters and the ESS: patients who considered themselves much or very much improved, also had the most improved breathing parameters and ESS score. No correlation was observed between PCGI-C and SART error score.

The majority of OSAS patients considered themselves improved after 8-week CPAP treatment. This improvement was best predicted by improved sleep-related breathing indices, as well as excessive daytime sleepiness scored by ESS. SART measurements of vigilance improved only marginally, not correlated to patient-rated clinical global improvement.

FUTURE PERSPECTIVES

The studies described in this thesis contribute to the validation of the SART as a parameter of treatment efficacy in sleep disorders with excessive daytime sleepiness. The SART proved to be robustly resistant against external influences such as time of day or taking a nap. We identified the optimal test instruction, improving discrimination between patients and healthy individuals. Additionally, the SART was able to detect treatment effects and correlated well with patient-rated improvement in type 1 narcolepsy, and proved to be complementary to measurements of sleepiness.

Nevertheless, additional studies are needed to further validate its use in other sleep disorders. Our OSAS study (Chapter 7) illustrates that its validity differs between sleep disorders. Our studies should preferably be replicated in other sleep laboratories, if possible using larger patient groups. This is especially important for the observational study of baseline SART measurements in various sleep disorders (Chapter 3), since the number of patients in this study varies between each reported group. Such a study should preferably include an individually matched control group.

First priority: replication of Chapter 4 in patients with various sleep disorders

In Chapter 4 we had investigated various aspects that may influence the SART, such as time of day, napping in between SART sessions, repetition effect and test instruction. Their effect should be investigated in patients with sleep disorders other than narcolepsy. The reason for this is that the associations between a specific instruction and the error count, or between the instruction and learning effect, need not be equally strong for patients and controls, nor for other sleep disorders. Type 1 narcolepsy is the only sleep disorder patient group for which a study with each test instruction has been performed. The error rate of patients with type 1 narcolepsy who received the instruction to pay attention to accuracy only was similar to that of patients with narcolepsy who received the instruction to pay equal attention to both accuracy and speed[1,8]. It seems likely that patients with narcolepsy function at their maximum capacity when instructed to pay equal attention to both accuracy and speed: their long RT suggests that they did not in fact pay equal attention to both aspects, but that they had sacrificed speed to maintain some accuracy.[8] In that case dropping the speed condition altogether would not improve accuracy. Their low level of accuracy[1], i.e. their inability to sustain attention for four minutes, quite probably reflects the problems narcoleptics face in daily life when trying to follow a conversation or read a book. Nevertheless, a direct comparison of test instruction in a group of narcolepsy patients should be preferred.

Moreover, such comparisons are required for other sleep disorders. Chapter 3 reported on SART performance in patients with idiopathic hypersomnia and obstructive sleep apnoea in addition to patients with narcolepsy. Subjects were instructed to pay equal attention to speed and accuracy. No control group was included. SART error count was visually compared to that of a historical healthy control group. In retrospect, this group turned out to be instructed to prefer accuracy over speed, so this comparison has its problems. Moreover, the study in Chapter 4 demonstrated that healthy controls might reach error counts similar to narcolepsy patients when instructed to pay equal attention to speed and accuracy as a result of the speed-accuracy trade-off. As a result, no inference may be made regarding the abnormality of the SART error count in patients with idiopathic hypersomnia and obstructive sleep apnoea in Chapter 3. These patients may possibly also function at maximum capacity when instructed to pay equal attention to both accuracy and speed. One indication that this held for narcolepsy patients is their long reaction time, observed even when subjects were instructed to pay equal attention to both accuracy and speed. The reaction times of healthy control subjects are significantly shorter when performing the SART with this test instruction. The reaction times of patients with idiopathic hypersomnia and obstructive sleep apnoea as described in Chapter 3 lie in between those of healthy controls and narcolepsy patients. As such, the two explanations for the abnormality of their error counts remain possible. Investigating the SART error count while instructing these patients to prefer accuracy to speed is therefore essential to understand whether vigilance impairment is indeed present in various sleep disorders.

The results of Chapter 4 were obtained after the studies in Chapters 5, 6 and 7 had been commenced. In the three latter studies, the SART had been administered with the instruction to pay equal attention to accuracy and speed. These studies comprise within-subject comparisons instead of a cross-sectional measurement. Narcolepsy patients seem to perform the SART poorly with both test instructions, so it is unlikely that the differences between pre-treatment and on-treatment conditions in Chapters 5 and 6 would have been even higher in case the instruction to prefer accuracy over speed had been provided. This explanation is not likely to hold true for Chapter 7. In that chapter, no clear improvement in SART performance had been observed in OSAS patients following CPAP treatment. Since a direct baseline comparison of OSAS patients and healthy controls was not performed, it remains unknown whether their baseline performance was abnormal. Indeed, their relatively high error rate could be the result of a strategy, since the patients were instructed to pay equal attention to accuracy and speed. A direct comparison with healthy controls remains therefore needs to be performed, preferably with the "accuracy first" instruction, as this optimises performance. If such a study would indicate a baseline difference between OSAS patients and healthy controls, then the CPAP treatment effect study would subsequently have to be replicated with the "accuracy first" instruction.

Second priority: SART accuracy parameters in future research

The SART parameters presented in this thesis are divided into accuracy measurements (commission error count, omission error count and total error count) and reaction time measurements (for instance average reaction time and reaction time variability). Only minor differences among the various accuracy measures of the SART were reported in Chapter 5, indicating that they reflect the same phenomenon. The highest effect size was found for the total error count. Statistically, the commission error count, i.e. the count of key presses when no key should have been pressed) was more reliable: this parameter was judged to yield reliable results when only two SART sessions were performed, compared to three for the total error count. The omission error count, i.e. the count of absent presses when a key should have been pressed), did not perform as well in terms of distribution and reliability. Still, the total error count did perform well, and, because it contains the omission error count as well, counting omission errors may have a role. The relative importance of omission, commission, and total error counts can differ between disorders.[9] The total error count was therefore chosen as primary outcome measure throughout this thesis. Nevertheless, it remains prudent to assess these error types separately when trying to replicate the findings of this thesis, especially when different patient groups are studied.

The SART in relation to other tests of sustained attention

Reaction times are recorded when performing the SART, as with other tests of sustained attention. We limited the number of reaction time parameters to two. The main value of the SART is to provide information about someone's capability to appropriately detect a change in stimuli to which an alternative response is needed, a function that is expressed through the error rate, more than through reaction time only. The influence of reaction time is minimised when using the "accuracy first" instruction. A practical disadvantage of a focus on reaction time is that measuring it accurately requires special equipment to exclude inaccuracies due to technical factors such as the monitor refresh rate or processing a mouse click. These factors cause inaccuracies that can vary over time, and therefore have the ability to unpredictably influence reaction time results. In contrast, measuring an error count only requires a standard personal computer. In case the main interest concerns simple reaction time measurements, then the PVT may suffice (preferably with special equipment for the reasons described above). This test has primarily been used and validated in sleep deprivation studies.[10-12] Studies in sleep disorders are scarce. Recently, baseline PVT results in patients with narcolepsy, idiopathic hypersomnia and behaviourally induced insufficient sleep syndrome were shown to differ from those of healthy controls.[13] In addition, the PVT is sensitive to treatment efficacy in obstructive sleep apnoea syndrome,[14] but its role in assessing treatment efficacy in narcolepsy was not proved in the study described in Chapter 6 of this thesis. In that study, the SART outperformed the PVT as a parameter of treatment effect measure in narcolepsy.

In the same study, we investigated the OSLER as a sustained attention task by adding behavioural outcome measures reflecting the level of vigilance before falling asleep. In fact, both the OSLER and PVT can be considered simple reaction time tasks. While the timing between stimuli varies from 2-10 seconds in the PVT, the stimuli of the OSLER are presented at a monotonous fixed rate. The sustained attention aspect of the OSLER, reflected by the parameter '$\text{OSLER}_{\text{OMISSIONS/MINUTE}}$', was more sensitive to the effects of sodium oxybate treatment than the PVT. Both the SART, measured in daily life, and OSLER, measured in the sleep laboratory, demonstrated capable of measuring treatment effects in narcolepsy. A direct comparison of both measures in the sleep laboratory would be interesting to assess the position of the OSLER as a sustained attention task.

Limitations of the SART

A major limitation of the SART is that a poor performance is not always due to a vigilance problem. Other explanations of poor performance include cognitive and motor problems. Cognitive disturbances that affect attention come into play, and any motor problem that affects reaction time may do so too. Accordingly, the importance of the SART is not that it is highly and purely sensitive to vigilance disturbances, but lies in the quantification of such impairments and its ability to compare situations, such as before and during treatment. It can be applied to quantify vigilance similarly as the MWT is applied to quantify sleepiness.

Performance on the SART is presumably influenced by motivational and environmental factors. If a test subject decides to perform poorly, the SART will show an abnormal response, so a poor performance may be the result of fraud. It is however nearly impossible to perform the SART abnormally well, so the test is resistant to fraud when it is important to perform well, as is the case for driving ability. The SART is therefore quite robust in this context, in contrast to the MWT, in which patients can use tricks to stay awake. Hence, the SART is suitable in situations where patients have a vested interest in performing well.

Position of the SART in future research and patient care

The studies in this thesis hopefully contributed to underline the importance of vigilance for patients with sleep disorders. We feel this is worthwhile, as advocated in the introduction in this thesis, as a vigilance impairment impacts functioning in daily life and may have serious safety implications, for instance regarding driving or working heavy machinery. In addition to the importance of vigilance impairment for individual patients, there are practical reasons to focus on measurements of vigilance rather than sleepiness. Currently used objective measurements of sleepiness such as MSLT and MWT require a laboratory setting. Clinical experience indicates that some patients feel their daytime functioning improved substantially due to stimulant drugs whereas their MWT improves hardly if at all. The non-arousing circumstances in the laboratory may impair the validity to the test to assess problems in the real world.

This thesis expands the understanding of essential practical prerequisites for a reliable and valid use of the SART in future studies and patient care, summarized by the following recommendations:

1. Five SART sessions prior to each of five MSLT sessions are recommended to quantify the level of vigilance for diagnostic purposes.
2. For other purposes we recommend to administer at least two SART sessions with 1.0-1.5 hour in between, preceded by a full training session. The time of day during regular working hours does not influence outcome.
3. Instructions to the patient should consist of the following: "A number from 1 to 9 will be shown 225 times in random order. You have to respond to the appearance of each number by pressing a button, except when the number is a 3. You have to press the button before the next number appears, but note that accuracy is more important than speed."
4. The following data should be recorded: the number of times a key was pressed when a 3 was presented (commission errors), the times when no key was pressed when it should have been (omission errors), and preferably also the reaction time of every correct press.

5. The SART error score is the preferred outcome measure and consists of the total number of errors, expressed as the sum of the commission and omission errors.

Recommendations 2 and 3 require further study in patients with sleep disorders, among which type 1 and 2 narcolepsy, idiopathic hypersomnia and obstructive sleep apnoea syndrome. Afterwards, vigilance measurements by means of the SART should form a cornerstone of future treatment efficacy studies of new drugs designed to improve daytime functioning. As an objective, functional outcome measure that correlates well with perceived improvement, the SART should at least be positioned as equally important as measurements focusing on sleepiness.

Vigilance measurement, by means of the SART, deserves to be more widely applied in studies of treatment efficacy in sleep disorders.

In addition to the role of the SART in assessing efficacy of drugs, it may well have a role in the assessment of fitness to drive. Dutch legislation on fitness to drive in patients with sleep disorders is currently based upon the opinion of a patient's functioning by an independent physician, supported by additional investigations depending on the sleep disorder. Patients with obstructive sleep apnoea syndrome should for instance have an apnoea-hypopnoea index under 15. However, functional outcome measures are not required. Patients with narcolepsy and idiopathic hypersomnia should have a mean sleep latency above eight minutes on the MWT and an ESS score under 11. In other words, they have to fulfil the requirements of two sleepiness measurements; no quantification of vigilance is required. Moreover, both measures of sleepiness have important disadvantages. Validity in real-world circumstances is not guaranteed. There is no evidence that MWT performance is a reliable predictor of risk of accident, although it does correlate to driving simulator performance in narcolepsy and OSAS.[15,16] In addition, the MWT is a costly investigation. In contrast, the ESS is a cheap and self-administered questionnaire on daily life situations, which does not share these disadvantages. However, the ESS is susceptible to voluntary efforts to perform better than usual, and is therefore not suitable as solitary additional test. As such, there is a need for novel parameters to support the physician's assessment of fitness to drive in patients with excessive daytime sleepiness. A crucial step in validation of the SART as a clinical tool in sleep medicine should therefore be to address the question whether the SART, both cheap and objective in nature, is a more reliable estimator of the risk of accident in the real-world situation than the MWT. To answer this question, SART and MWT performance should preferably be compared to a driving test on the road, taken by a driving instructor or examiner.

Driving simulator performance may aid to the comparison, but should not be the only test of real driving performance.

The SART may prove suitable as a tool to assess fitness to drive in patients with sleep disorders. In addition to its validity to quantify treatment effects, it does not share some major disadvantages of the currently applied tests: it is cheap, easy to administer, and quite robust against attempts to perform better than in a real life situation.

REFERENCES

1. 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.
2. 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.
3. Manly T, Robertson IH, Galloway M, Hawkins K. The absent mind: further investigations of sustained attention to response. *Neuropsychologia.* 1999;37(6):661-670.
4. Helton WS, Weil L, Middlemiss A, Sawers A. Global interference and spatial uncertainty in the Sustained Attention to Response Task (SART). *Conscious Cogn.* 2010;19(1):77-85.
5. Shalgi S, O'Connell RG, Deouell LY, Robertson IH. Absent minded but accurate: delaying responses increases accuracy but decreases error awareness. *Exp Brain Res.* 2007;182(1):119-124.
6. McAvinue L, O'Keeffe F, McMackin D, Robertson IH. Impaired sustained attention and error awareness in traumatic brain injury: implications for insight. *Neuropsychological Rehabilitation.* 2005;15(5):569-587.
7. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *Lancet neurology.* 2013;12(11):1068-1075.
8. Van Schie MK, Thijs RD, Fronczek R, Middelkoop HA, Lammers GJ, Van Dijk JG. Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness. *Journal of Sleep Research.* 2012;21(4):390-395.
9. Hart EP, Dumas EM, Reijntjes RH, et al. Deficient sustained attention to response task and P300 characteristics in early Huntington's disease. *Journal of neurology.* 2012;259(6):1191-1198.
10. 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.
11. Dinges DF, Powell JW. Sleepiness is more than lapsing. *Sleep Res.* 1988;17(84).
12. 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.
13. 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.

14. Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Med* 2003;5(5):393-402.
15. 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.
16. Philip P, Chaufton C, Taillard J, et al. Maintenance of Wakefulness Test scores and driving performance in sleep disorder patients and controls. *Int J Psychophysiol.* 2013;89(2):195-202.