Attention please: vigilance in patients with excessive daytime sleepiness

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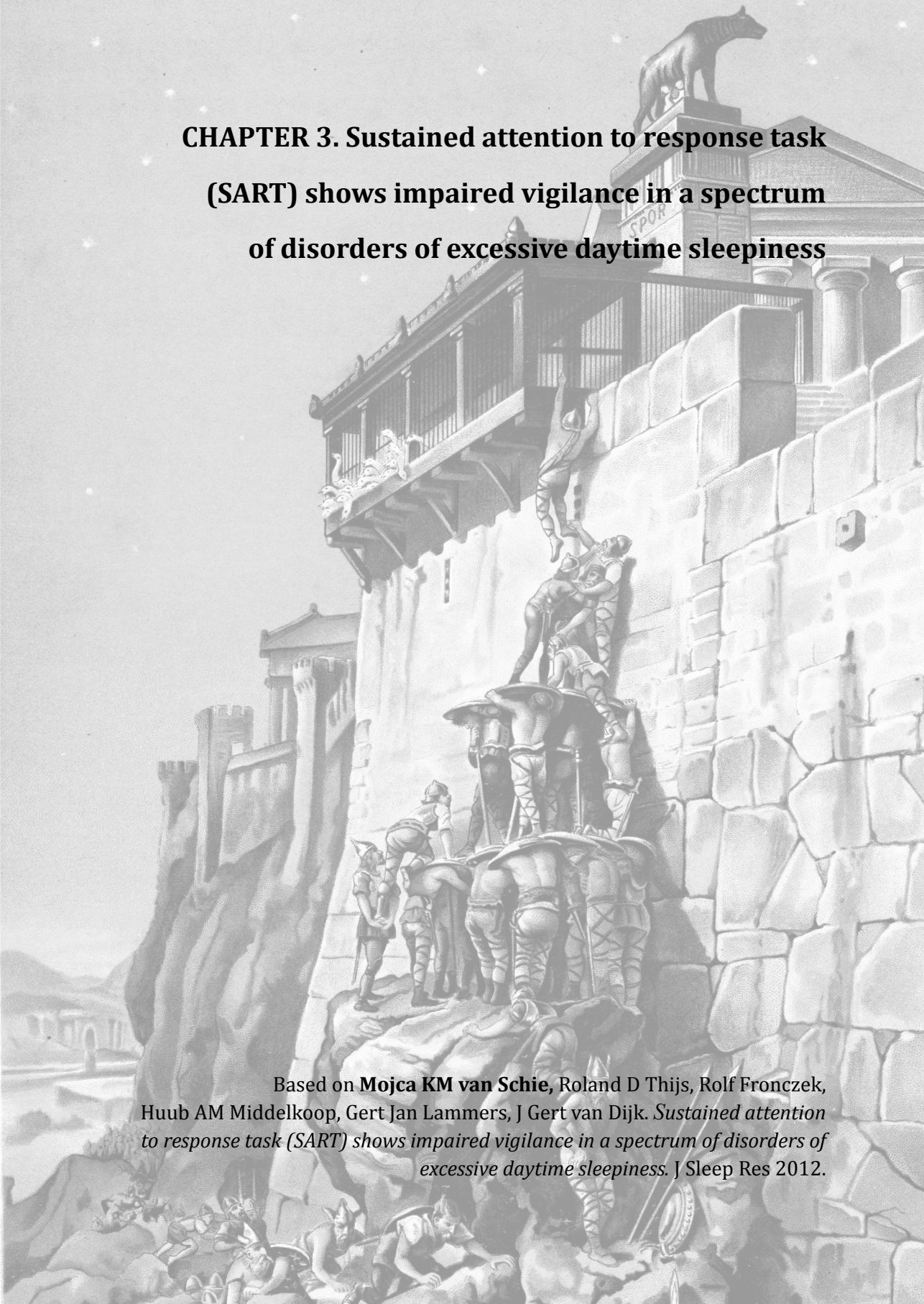

CHAPTER 3. Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness

Based on **Mojca KM van Schie,** Roland D Thijs, Rolf Fronczek, Huub AM Middelkoop, Gert Jan Lammers, J Gert van Dijk. *Sustained attention to response task (SART) shows impaired vigilance in a spectrum of disorders of excessive daytime sleepiness.* J Sleep Res 2012.

SUMMARY

The Sustained Attention to Response Task (SART) comprises withholding key presses to 1 in 9 of 225 target stimuli; it proved to be a sensitive measure of vigilance in a small group of narcoleptics. We studied SART results in 96 patients from a tertiary narcolepsy referral centre. Diagnoses according to ICSD-2 criteria were narcolepsy with (n = 42) and without cataplexy (n = 5), idiopathic hypersomnia without long sleep time (n = 37), and obstructive sleep apnoea syndrome (n = 12). The SART was administered prior to each of 5 MSLT sessions. Analysis concerned error rates, mean reaction time (RT), RT variability and post-error slowing, as well as the correlation of SART results with mean latency of the Multiple Sleep Latency Test (MSLT) and possible time of day influences. Median SART error scores ranged from 8.4 to 11.1, and mean RTs from 332 to 366 ms. SART error score and mean RT did not differ significantly between patient groups. SART error score did not correlate with MSLT sleep latency. RT was more variable as the error score was higher. SART error score was highest for the first session. We conclude that a high SART error rate reflects vigilance impairment in excessive daytime sleepiness irrespective of its cause. The SART and the MSLT reflect different aspects of sleep/wakefulness and are complementary.

INTRODUCTION

Excessive daytime sleepiness (EDS), an increased tendency or need to fall asleep (International Classification of Sleep Disorders, 2005), is the key symptom of many sleep disorders. In narcolepsy, EDS is accompanied by vigilance impairment, leading to impaired performance in the waking state (Broughton *et al.*, 1982). A previous small study by our sleep lab showed that impaired vigilance in narcolepsy could be quantified with the Sustained Attention to Response Task (SART) ((Fronczek *et al.*, 2006). This test is explained in the methods section; in short, it involves pressing a key when a number (1 to 9) appears on a screen except when that number is a 3. The main outcome is the total error score, consisting of both key presses when no key should be pressed and the reverse. In our previous study the total error score had shown excellent sensitivity (87%) and specificity (100%) in a comparison of 15 patients with narcolepsy and cataplexy and 15 healthy controls. The diagnostic yield was in fact as good as that of the Multiple Sleep Latency Test (MSLT). The mean SART error score was not related to the mean MSLT sleep latency, suggesting that the two approaches measure different aspects: the SART, requiring prolonged attention, likely reflects impaired vigilance, while the MSLT measures the propensity to fall asleep quickly.

Based on these promising results, we investigated vigilance impairment with the SART in a prospective sample of patients with various causes of EDS. The study focused on the mean error score as the mean parameter of interest. Additional questions were the correlation between SART and MSLT results, analysis of reaction time (RT) data and possible time-of-day influences on test results.

MATERIALS AND METHODS

Patients

Our department is a tertiary referral centre for suspected hypersomnias of central origin. The routine work-up comprised a diagnostic interview, nocturnal polysomnography the night before MSLT, SART and MSLT for all patients.

Patients with a complaint of EDS referred for suspected hypersomnias of central origin were included if diagnosed with a sleep disorder based on ICSD-2 criteria (International Classification of Sleep Disorders, 2005). Any other ancillary investigations necessary for ICSD-2 diagnosis were not investigated in the present study. Patients evaluated for driving ability were excluded from this study, as were patients who used stimulants on the day of testing.

In accordance with Dutch law, patients gave oral consent to this routine work-up. The research has not been presented to an Ethics Committee for a review, as Dutch

law states that this is not necessary for research with data that were originally gathered for patient care and afterwards anonymously used by their treating physicians in retrospective case-studies.

The MSLT consisted of five sessions of 20 minutes with a 1.5-hour break in between. The first session started at 09:00 hrs (Carskadon *et al.*, 1986).

Sustained Attention to Response Task

Patients underwent a 4-minute-20-second taking SART session prior to each of five MSLT sessions during one day as described previously (Fronczek *et al.*, 2006). The SART was administered while subjects were seated in front of a computer screen in a quiet room. Before the first session all subjects performed a short version of the SART to become familiar with the test. Between sleep latency tests, participants were allowed to go for short walks in the hospital and eat or drink, but they were not allowed to sleep or use stimulating agents.

In short, the SART comprises the numbers 1 to 9 appearing 225 times in random order and in different sizes in a white font on a black computer screen. Subjects had to respond to the appearance of each number by pressing a button except when the number was a 3, which occurred 25 times in all. Subjects had to press the button before the next number appeared and were instructed to give equal importance to accuracy and speed in performing the task (Manly *et al.*, 1999; Robertson *et al.*, 1997). 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 appearance of the numbers on a cathode ray tube screen was timed using a dedicated video graphics array switch to avoid delays of uncertain magnitude due to build-up of screen data. The resulting maximal uncertainty was 10 milliseconds, allowing reaction times (RT) to be measured with sufficient accuracy. The following measures of response accuracy were assessed: the number of commission errors, with a maximum of 25; the number of omission errors, with a theoretical maximum of 200 errors. The 'SART error score' represents the sum of the numbers of commission and omission errors.

The following measures of reaction time (RT) were assessed (Picton *et al.*, 2007; Stuss *et al.*, 2003): These were the mean RT in ms, calculated over correct response trials, i.e., key presses after anything but a '3'. RT variability was quantified as the coefficient of variation of RT for correct response trials: this is the standard deviation divided by the mean RT of that test. RT often increases temporarily following a commission error in various choice-response tasks (Dudschig and Jentzsch, 2009; Notebaert *et al.*, 2009; Rabbitt, 1966). This 'post-error slowing' was calculated as follows: The last RT before a commission error was noted as was the first one after it. The difference between the later and the earlier RT was divided by the mean RT of that session.

Statistical analysis

Differences between groups were studied for all six SART outcome measures. For each subject, the means of 5 MSLT sleep latencies and SART scores were computed and used in the analysis. The non-parametric Kruskal-Wallis test was employed to compare SART outcome measures between groups.

The correlation between mean MSLT sleep latency and the SART error score was assessed using Spearman's ρ, since variables were not normally distributed. Correlations of MSLT sleep latency with the numbers of commission and omission errors were assessed.

A higher number of commission errors has previously been demonstrated to correlate with shorter RT (Helton *et al.*, 2010; Manly *et al.*, 1999; Robertson *et al.*, 1997; Shalgi *et al.*, 2007), indicating that errors on the SART should be interpreted along with RT measures. Therefore, the correlation between SART RT measures and SART accuracy measures was assessed using Spearman's ρ. A paired t-test was used to determine whether RT before and after a '3' differed significantly differed, both for a correct response (no key press) and for a commission error.

Effects of testing time on SART error score were evaluated using the Friedman-Test with post-hoc analysis after Conover (Conover, 1980).

RESULTS

Patients

One-hundred twelve patients who were evaluated for EDS between February 2006 and March 2010 met the inclusion criteria. Sixteen of these were excluded due to simultaneous evaluation of driving ability. Ninety-six patients were included, of whom 16 used antidepressants.

Patients were classified in four groups based on diagnosis: narcolepsy with and without cataplexy, idiopathic hypersomnia without long sleep time, and obstructive sleep apnoea syndrome (OSAS) (Table 1). Patient groups differed significantly for the ratio of men to women ($p < 0.02$) and age ($p < 0.01$). The narcolepsy-without-cataplexy group consisted entirely of men. OSAS patients were significantly older than those in other groups. Patient groups did not differ in the proportion of patients who continued the use of anti-depressant medication on the day of MSLT and SART ($p > 0.52$).

SART results

SART and MSLT data for each patient group are presented in Table 2. Neither the median SART error score ($H(3) = 1.66$ $p > 0.64$) nor the numbers of commission ($H(3) = 2.15$ $p > 0.54$) and omission errors ($H(3) = 2.69$ $p > 0.44$) differed significantly between groups.

The same held for mean RT ($p > 0.55$), RT variability ($p > 0.65$) and post-error slowing ($p > 0.41$). After correction for age and gender, SART accuracy measures and RT measures still did not differ between groups. Figure 1 illustrates SART error score findings per group next to findings in healthy controls from our previous study (Fronczek *et al.*, 2006) illustrating the magnitude of the differences in sleep latencies on MSLT and lower error scores on SART compared to all patient groups, while not serving as a direct comparison with the groups in the current study.

Fig. 1a MSLT sleep latencies of patient groups and controls

Fig. 1b SART error scores of patient groups and controls

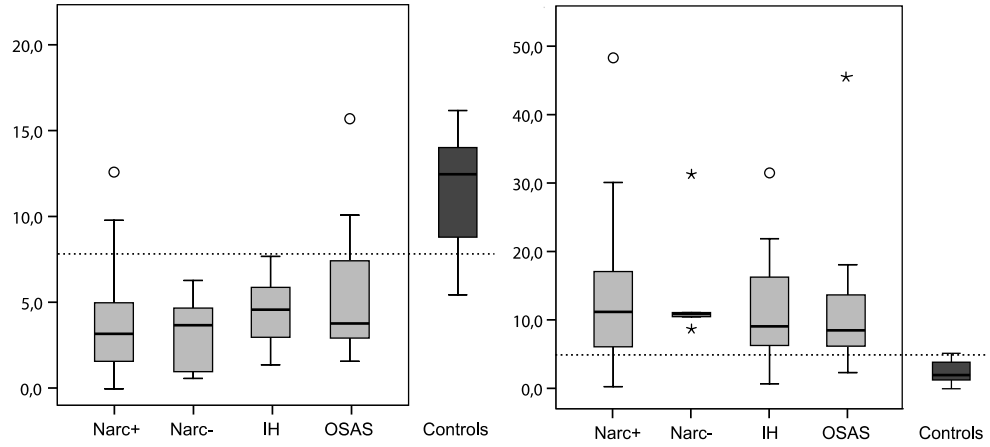

Figure 1– Mean of five Multiple Sleep Latency Test sleep latencies in minutes (a) and Sustained Attention to Response Task error scores (b) on the assessment day for all patients, with separate box plots representing each patient group, and for controls from our pilot study.
Narc+: narcolepsy with cataplexy; Narc-: narcolepsy without cataplexy; IH: Idiopathic Hypersomnia; OSAS: Obstructive Sleep Apnea Syndrome. The horizontal dotted lines represent cut-off values for MSLT (8 minutes) and SART (5 errors) (Fronczek *et al.*, 2006).

Table 1 – Group characteristics

Patient group	N	Age in years (SD)	% of males	Antidepressant use (N)
Narcolepsy with cataplexy	42	37.5 (19.1)	50.0	7
Narcolepsy without cataplexy	5	43.8 (20.3)	100.0	2
Idiopathic Hypersomnia	37	44.2 (15.0)	43.2	5
OSAS	12	57.4 (14.5)	83.3	2
Total	96	42.9 (18.0)	54.2	

Legend: OSAS: Obstructive Sleep Apnea Syndrome.

Table 2 - MSLT and SART outcome measures by patient group

	Narc. + cata (n=42)		**Narc. - cata (n=5)**		**IH (n=37)**		**OSAS (n=12)**	
MSLT	*Median*		*Median*		*Median*		*Median*	
	25th-75th perc.		*25th-75th perc.*		*25th-75th perc.*		*25th-75th perc.*	
latency (min)	3.2	1.5-5.0	3.0	1.2-5.6	4.6	3.0-5.9	3.8	2.9-7.9
REM (n)	2	1-4	4	4-5	0	0-0	0	0-0
SART accuracy meas.	*Median*		*Median*		*Median*		*Median*	
	25th-75th perc.		*25th-75th perc.*		*25th-75th perc.*		*25th-75th perc.*	
comm./25	8.1	4.6-12.6	9.8	8.5-15.5	7.4	4.9-11.3	8.1	6.1-10.3
omiss./200	1.4	0.4-4.4	1.0	0.4-6.2	1.0	0.2-2.7	0.6	0.0-2.3
err.sc./225	11.1	6.0-17.4	10.8	9.5-21.1	9.0	5.9-16.3	8.4	6.1-14.3
SART RT meas.	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*
mean RT (ms)	337	(83)	332	(74)	359	(82)	366	(87)
RT var. (ms)	0.30	(0.10)	0.32	(0.14)	0.29	(0.07)	0.28	(0.07)
PES (ms)	0.16	(0.22)	0.03	(0.21)	0.11	(0.15)	0.10	(0.17)

Legend: Narc.: Narcolepsy; +/- cata: with/without cataplexy; IH: Idiopathic Hypersomnia; OSAS: Obstructive Sleep Apnea Syndrome; latency: MSLT sleep latency time; min: minutes; REM: number of MSLT sessions in which REM-sleep was recorded; meas: measures; comm.: total number of commission errors; omiss.: total number of omission errors; err.sc.: SART error score; RT var.: RT variability; PES: post-error slowing, perc.: percentiles.

SART-MSLT correlates

No significant correlation was found between SART error score and mean MSLT sleep latency for all 96 patients together, or between the number of SART commission errors and MSLT sleep latency. The number of omission errors, however, was significantly and inversely correlated with MSLT sleep latency ($r_s = -0.24$, $p < 0.02$).

Analysis of SART outcome measures

Greater RT variability was strongly associated with higher SART error score ($r_s = 0.76$, $p < 0.01$). No significant correlation between mean RT and SART error score was found ($r_s = -0.07$, $p = 0.5$), but mean RT was significantly correlated with the number of commission errors ($r_s = -0.38$, $p < 0.01$).

Making errors influenced RT (Figure 2). After a correctly withheld no-go trial (a '3'), a significant decrease in RT occurred ($p < 0.01$). However, when a '3' was incorrectly responded to by a key press, the RT afterwards was increased ($p < 0.01$).

Fig. 2a Reaction times before and after a correct response (no key press)

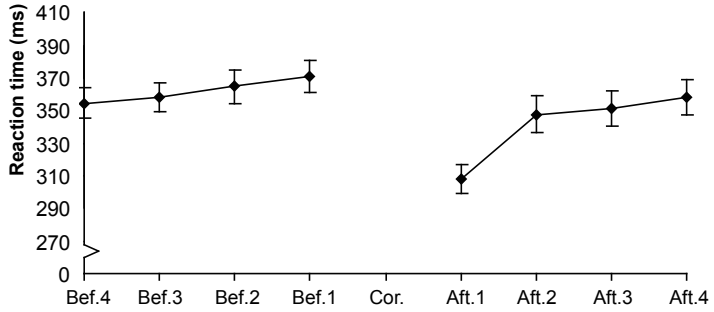

Fig. 2b Reaction times before and after a commission error

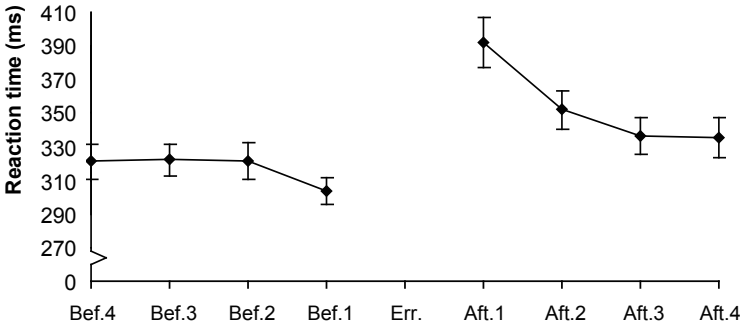

Figure 2– Mean Sustained Attention to Response Task reaction times on 4 trials before and 4 trials after a correct withhold (a) and a commission error (b) on a no-go trial.
Bef.4 = 4th trial before a no-go trial. Aft.1= 1st trial after a no-go trial. Cor. = correct withhold. Err. = commission error. Error bars indicate SEM.

Time-of-day influences on SART error score

SART error scores differed significantly between sessions ($p < 0.02$), with session 1 showing the highest error scores. Post-hoc testing showed that SART error score for the first session differed significantly with that of all but the third sessions. The diurnal variation of SART error score per patient group is shown in figure 3.

SART error score fluctuations between sessions

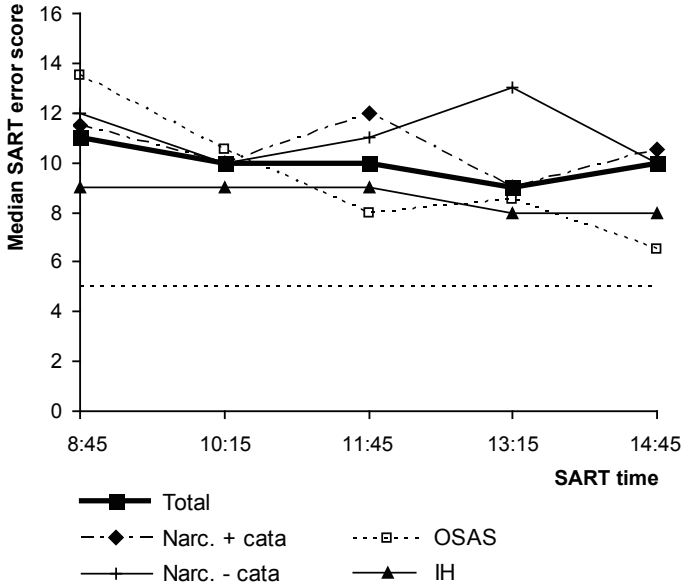

Figure 3 – Median Sustained Attention to Response Task error score at 5 testing times on one day. SART error score was significantly higher at the 8:45 session than at other sessions except 11:45. Narc.: Narcolepsy; +/- cata: with/without cataplexy; IH: Idiopathic Hypersomnia; OSAS: Obstructive Sleep Apnea Syndrome. The horizontal dotted line at SART error score of 5 errors marks the cut-off value for abnormal SARTs previously found in a study of narcoleptics and healthy controls (Fronczek *et al.*, 2006).

DISCUSSION

In this cross-sectional study, we investigated the SART as a tool to measure vigilance in patients with different causes of EDS. The main finding was a high SART error rate in all patient groups. Patient groups did not differ in median SART error score or in other SART outcome measures. This confirms our previous suggestion that the SART error score does not reflect any specific disease entity. Instead, SART error score probably reflects a key symptom of all sleep-related disorders that were studied, i.e., vigilance impairment.

SART-MSLT correlates

Regarding SART-MSLT correlates, we did not find a significant correlation between SART error score and MSLT sleep latency. The lack of a relationship confirms our previous findings (Fronczek *et al.*, 2006) and underlines that the SART and the MSLT measure different phenomena, i.e., the SART is a distinct parameter of disease burden in sleep

disorders. We expanded the study to include commission and omission errors. Somewhat surprisingly, the number of omission errors correlated significantly and inversely with MSLT sleep latency; in other words: those who often failed to press a key after frequently occurring stimuli fell asleep quickly. This correlation resembles the one found between MSLT sleep latency and cumulative increase in performance lapses at the psychomotor vigilance task (PVT) (Carskadon and Dement, 1981; Dinges *et al.*, 1997). SART omission errors may thus have an analogue in PVT attentional lapses. However, the SART, unlike the PVT, requires subjects to decide whether a response is needed or not for each stimulus. As such, the SART, in including response inhibition, assesses an additional component of vigilance (Helton, 2009; Manly *et al.*, 1999; O'Connell *et al.*, 2009).

Impaired SART parameters and sleep disorders

What could be the mechanism for impaired SART parameters in sleep disorders? Molenberghs *et al.* (2009) found indications for decreases in SART scores in patients with frontal brain deficits. These indications of associations between SART parameters and frontal brain regions may reflect the decision-making component of the SART. Falling asleep is associated with inhibiting basal forebrain and brainstem arousal systems, the former being responsible for excitatory projections into, among others, the frontal cortex (Sherin *et al.*, 1998; Steininger *et al.*, 1999; Uschakov *et al.*, 2007). Through these projections, sleep disorders with hypersomnia may affect frontal cortical arousal. In fact, frontal cortical gray matter loss and frontal brain activation changes have been found in various sleep disorders (Ayalon *et al.*, 2006; Ayalon *et al.*, 2009; Brenneis *et al.*, 2005; Kaufmann *et al.*, 2002; Sherin *et al.*, 1998; Steininger *et al.*, 1999; Uschakov *et al.*, 2007). Hence, from a speculative point of view, high error score found in sleep disorders might be explained by changes in frontal functions. However, neuroimaging studies of patients with sleep disorders are needed to help address this hypothesis.

RT measurements in the SART

Correlating SART error score with RT measures showed that errors were more frequent when RT variability was larger. This latter finding may simply reflect impaired vigilance, which can lead to lapses of attention, causing fluctuations in RT as well as an increase in both omission errors (severe response 'lapses') and commission errors (Braver *et al.*, 2003; Duncan *et al.*, 1996; Stuss *et al.*, 1995; Wilkins *et al.*, 1987).

In agreement with the literature (Helton *et al.*, 2010; Manly *et al.*, 1999; Robertson *et al.*, 1997; Shalgi *et al.*, 2007), the number of commission errors was inversely correlated with mean RT. This has previously been explained as the so-called speed-accuracy trade-off, which presumes an influence of task strategy on the SART error score. Therefore, it would be valuable to know whether different instructions affect SART performance in EDS and whether equal importance is given to speed and accuracy.

Time-of-day influences on SART error score

We found diurnal effects on SART performance with the highest SART error score at the first session in the morning. This higher error score may still reflect a brief learning period or an underlying time-of-day effect and thus requires further study.

Strengths and limitations

A strength of this study is the large size of the patient group with several causes of EDS. In addition this study focused on reaction time as well as the more frequently studied accuracy measurements.

The most important limitations are the lack of individually matched controls and limited size of some of the groups. However, we did confirm the high SART error score data in a larger cohort of narcolepsy patients and demonstrated that SART outcome measures do not differ between patients with various causes of EDS.

CONCLUSION

Vigilance, as quantified by the SART, is as impaired in narcolepsy, as in other EDS causes. Yielding different results, SART is complementary to MSLT and does not only provide information about reaction time, as PVT does, but also about the capability of decision-making. The SART is easy to administer, cheap, and takes little time to perform. Combining SART and MSLT has the potential to become an important tool in clinical practice, as the combined approach yields information not only about the propensity to fall asleep, but also about performance in the waking state. Further studies are needed to assess the correlation between subjective impression of vigilance and objective SART outcome, and to probe the ability of the SART to measure treatment effect.

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