Hypocretin deficiency : neuronal loss and functional consequences

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Focusing on Vigilance instead of Sleepiness in the Assessment of Narcolepsy: High Sensitivity of the Sustained Attention to Response Task (SART)

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CHAPTER 7

Focusing on Vigilance Instead of Sleepiness in the Assessment of Narcolepsy: High Sensitivity of the Sustained Attention to Response Task (SART)

Context The severity of narcolepsy is commonly measured with the Multiple Sleep Latency Test (MSLT), focusing on the tendency to fall asleep. A neglected but perhaps equally important complaint is impaired performance in the waking state. We evaluated the Sustained Attention to Response Task (SART) for the quantification of vigilance in narcolepsy.

Methods The SART involves withholding key presses to 1 in 9 target stimuli. In the present study, it was administered prior to each of 5 MSLT sessions in a 1-day study. The Epworth Sleepiness Scale was administered to measure subjective sleepiness. SART and MSLT results (number of errors and sleep latency) were compared using Receiver Operator Curves, sensitivity, and specificity.

Patients Fifteen untreated narcoleptics and 15 matched controls.

Results The area under the receiver operating curve was 0.97 for the MSLT and 0.95 for the SART. Sensitivity and specificity for the MLST were 80% and 100% using a cutoff point of 5 minutes. For the SART, these values were 87% and 100%, using a 5-error cutoff. The SART and MSLT showed no correlation with each other or with the Epworth Sleepiness Scale.

Conclusion The SART, measuring attention, was abnormal as often as the MSLT, measuring sleepiness. The inability to remain vigilant during the day may be the most serious complaint in narcolepsy, since it impairs performance. The SART is valid in this respect, is easy to administer, and takes little time.

Introduction

Excessive daytime sleepiness (EDS), usually characterized as the tendency to fall asleep, is considered to be the main complaint in narcolepsy. However, this focus on inadvertently falling asleep may have led to undervaluation of a perhaps equally important complaint: impaired performance in the waking state. Broughton et al reported in the early 1980s that impaired performance in narcolepsy was linked not only to sleep but

also to lapses in vigilance.[1-3] Fluctuations in vigilance in narcolepsy may be considered as the counterpart of fragmented nocturnal sleep. In fact, the notion that both sleep and vigilance are disturbed has led to the concept of a loss of "state boundary control" to explain the pathophysiology of narcolepsy.[4,5] Moreover, a combined deficit of sleep and vigilance control has emerged as the core problem in narcolepsy in hypocretin-deficient mice.[6] In spite of the importance of the dual disturbance of vigilance and sleep, the most commonly used tests to measure the severity of narcolepsy focus solely on the tendency to fall asleep. The multiple sleep latency test (MSLT) is the most commonly used objective test to assess sleepiness and to diagnose narcolepsy.[7] Sleep latency is measured in 4 or 5 twenty-minute periods over 1 day, during which subjects lie in a dark and quiet room and try to fall asleep. Narcolepsy is likely when the mean sleep latency is 5 minutes or less and 2 or more sleep-onset rapid eye movement (REM) periods occur. Some authors have recently advocated an abnormality threshold of 8 minutes.[8] Various studies have questioned both the diagnostic yield and the validity of the MSLT in the diagnosis of narcolepsy.[8-14] For example, patients without sleep complaints may fulfil MSLT criteria for narcolepsy, whereas only 70% of patients with clear cataplexy do.[13,15] Although the mean sleep latency may well quantify sleepiness in healthy sleepdeprived subjects, it is debated whether it does so in narcolepsy.[9,14] On top of these limitations, the MLST is time and labor intensive. The maintenance of wakefulness test (MWT) is an alternative to the MSLT. Subjects are asked to remain awake instead of trying to fall asleep, which may better reflect daily life.[16] However, the validity of the MWT is also questionable, and it is equally time consuming to perform.[9,17] Therefore, the time seems ripe for tests aimed at impaired vigilance to measure this aspect of the severity of narcolepsy. Such a test may also have better properties to predict impaired performance.

We considered the Sustained Attention to Response Task (SART) to be a good candidate, since it reflects vigilance and sustained attention.[18,19] Furthermore, it only takes a short time to perform, has a high frequency of stimuli, and is easy to administer, which make it useful in a clinical setting. To explore the role of the SART in diagnosing and quantifying vigilance as an essential aspect of the severity of narcolepsy, we compared the SART with 2 current tools to measure sleepiness: the MSLT and the Epworth Sleepiness Scale (ESS).[20]

Materials and methods

Subjects

Fifteen unmedicated patients with narcolepsy were studied; all had daytime sleepiness and unequivocal cataplexy and thereby fulfilled the criteria of narcolepsy with cataplexy (International Classification of Sleep Disorders).[21] Thirteen patients were tested shortly after diagnosis and had never had treatment. Two patients had stopped medication to participate. These 2 patients were the only ones who had previously undergone an MSLT, but their diagnosis did not rely on MSLT results, as both had clear cataplexy. Unmedicated controls were recruited using an advertisement in a local newspaper and were matched in number, sex, age, and level of education with the patients. No

control had any complaints of excessive sleepiness or lowered vigilance. All subjects were instructed to follow their normal sleep routine the night before the testing day.

Design

The ESS was administered at 8:30 AM. This is a simple self-administered questionnaire, which is shown to provide a measurement of the subject's general level of daytime sleepiness.[20] The first sleep latency test began at 9:00 AM. The MSLT was performed according to the standards laid out by Carskadon et al,[22] with sleep latency tests at 9:00 AM, 10:30 AM, 12:00 noon, 1:30 PM, and 3:00 PM. The SART (see below) was administered 15 minutes prior to each sleep latency test, while subjects were seated on a chair in front of a computer screen. Before the sleep latency test at 9:00 PM, all subjects had to do 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 not sleep.

Table 1—Clinical Characteristics and Test Results

	Controls	**Narcolepsy**
Men/women, no.[a]	9/6	8/7
Age, y	34 (28-39)	33 (30-36)
ESS score	4.3 (2.6-7.0)*	17.4 (16.1-19.8) *
SART error score	2.0 (1.3-4.0)*	10.6 (6.1-18.7)*
MSLT sleep latency, min	12.2 (8.6-14.2)*	2.5 (0.8-4.7*

Data are presented as medians with 25th and 75th percentile in parentheses unless otherwise indicated. ESS refers to Epworth Sleepiness Scale; SART, Sustained Attention to Response Task; MSLT, Multiple Sleep Latency Test.
Mann-Whitney U was used to assess group differences; *$p < .01$
[a]χ^2 test was used to assess group differences; *$p < .01$

Sustained Attention to Response Task

A number from 1 to 9 was shown 225 times in white on a black computer screen over a 4.3-minute period in a quiet room with dimmed lights. Each of the 9 numbers was shown 25 times in random order. The font size was chosen at random from 26, 28, 36, or 72 points. The numbers were presented in a predetermined and quasirandom way so that identical numbers were not clustered. Each number was presented for 250 milliseconds, followed by a blank screen for 900 milliseconds. Subjects had to respond to the appearance of each number by pressing a small button, except when the number was a 3. Subjects had to press the button before the next number appeared and were instructed that accuracy was more important than speed. A complete SART takes 4 minutes and 20 seconds to perform. The SART error score consists of the total number of errors, expressed as the sum of the times a key was pressed when a 3 was presented, and the times when no key was pressed when it should have been.

Statistical Analysis

Differences between groups were assessed using the Mann-Whitney test. For each subject, the mean of the 5 MSLT latencies and SART scores were computed and used in

the analysis. Receiver operator curves (ROC) were employed to compare the diagnostic yield of the MSLT and the SART. Sensitivity and specificity were computed using the commonly used 5- and 8-minute cutoffs for the MSLT. For the SART a 5-error cutoff point was used, which was derived from the 95th percentile in controls (5.4 errors). As variables were not normally distributed, Spearman ρ was used to investigate the correlation within the separate groups between the MSLT, the SART, and the ESS. Effects of testing time were first evaluated using the Friedman-Test and analyzed posthoc using the Wilcoxon Signed Rank Test.

Results

Test Results

Data are presented as median (25th-75th percentile). The median sleep latency was 2.5 (0.8-4.7) minutes in patients and 12.2 (8.6-14.2) minutes in controls (Figure 7.1a). Controls showed a broader range (12.6 minutes) in MSLT sleep latencies than patients (8.0 minutes). The median SART error score was 10.6 (6.1-18.7) errors for patients and 2.0 (1.3-4.0) errors for controls (Figure 7.1b). SART error scores of patients showed a much broader range (33.0 errors) than did error scores of controls (5.0 errors). On the ESS, patients obtained a median score of 17.4 (16.1-19.8), whereas controls had a median score of 4.3 (2.6-7.0). The differences between patients and controls were significant for all these tests ($p < .01$; Table 1).

In contrast with that of the patient group, the sleep latency significantly differed between testing times in the control group (controls: $p < .01$, patients: $p = .59$; Figure 7.2a). In controls, the sleep latency at noon was significantly shorter, as compared with the sleep latency at 9:00 AM and 10:30 AM (9:00 AM: $p < .01$, 10:30 AM: $p = .04$). In controls, the SART error score significantly differed between testing times. This effect was not significant in patients (controls: $p < .01$; patients: $p = .46$; Figure 7.2b). In controls, the SART error score at 9:00 AM was higher, as compared with the SART error scores at all other testing times (all testing times: $p < .02$).

Diagnostic Yield

Areas under the ROC were 0.97 for the MSLT and 0.95 for the SART. The sensitivity and specificity for the MSLT were 80% and 100% using a 5-minute cutoff. With an MSLT cutoff point at 8 minutes (stage 1), sensitivity and specificity for the MSLT were 93% and 80%. For the SART, these were 87% and 100%, using the 5 error cutoff.

Correlations

No significant correlation emerged between SART error score and MSLT latency in either controls or patients (controls: $\rho=0.29$, $p = .33$; patients: $\rho = 0.15$, $p = .60$; Figure 7.3). No correlations between the SART error score, the MSLT latency, or the ESS were significant (all: $\rho < .27$, $p > .33$).

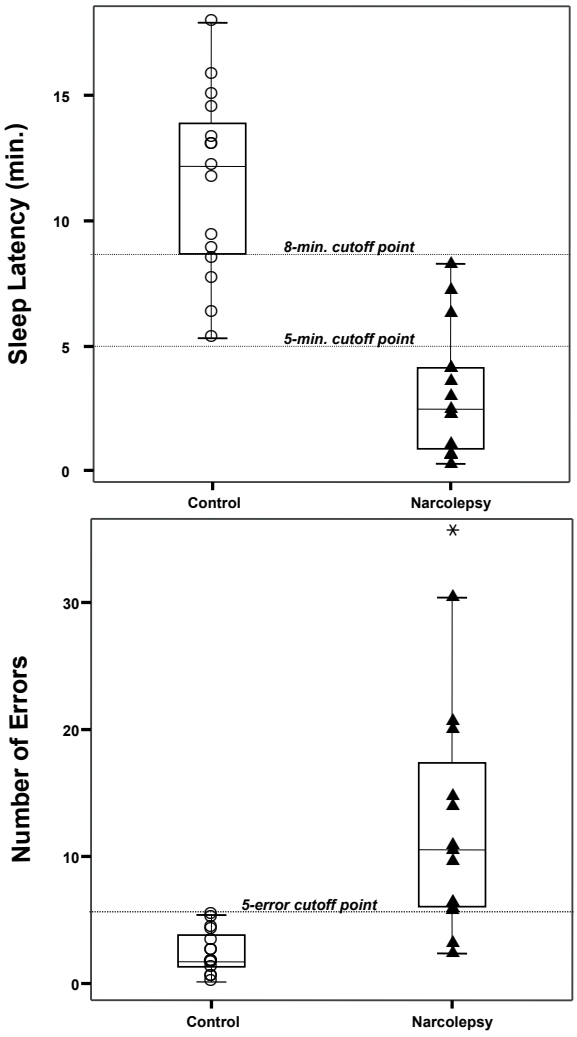

Figure 7.1
Boxplots
Multiple Sleep Latency Test (MSLT) sleep latency (a) and Sustained Attention to Response Task (SART) error score (b). This figure shows box plots indicating the median, 25th-75th percentiles, and the range. An asterisk indicates an out-of-range value. With cutoff points for the MSLT and SART, respectively, at 5 minutes (stage I) and 5 errors, sensitivity and specificity for the MLST were 80% and 100%. For the SART, these were 87% and 100%. With an MSLT cutoff point at 8 minutes (stage I), sensitivity and specificity for the MSLT were 93% and 80%.

Discussion

In this explorative study, we investigated the SART as a tool to measure vigilance as an important indicator of the severity of narcolepsy and compared it to the MSLT, known to reflect the tendency to fall asleep. In their respective roles, both tests performed equally well, as shown by excellent ROC and high sensitivity and specificity. There was clear evidence that both tests indeed measured different phenomena: there was no correlation between MSLT and SART results. Moreover, the range of MSLT latency was considerably larger in controls than in patients, while the reverse applied to an even stronger degree for the range of SART error scores. The large variability of SART results in patients may be advantageous, in that it may offer a better resolution to quantify vigilance as a severity indicator of narcolepsy, which may be of use in measuring treatment effects.

Our results are in line with Broughton and colleagues, who found that narcoleptic patients have more lapses (response omissions) and false-positive responses (errors of commission) during the Wilkinson Auditory Vigilance Task.[2] The SART error score consists of the sum of errors of omission as well as those of commission. Another benefit of the SART is that it is considerably shorter than other vigilance tasks, while having a high resolution to analyze vigilance. Subjects have to respond to a continuous sequence of stimuli but have to inhibit a response at an unexpected moment. In contrast, most vigilance tests consist of responding to unexpected stimuli over a longer time period. In the time between stimuli, no action by the subject is required and, as such, no information about the level of vigilance in these periods is acquired. How well does the SART compare with the ESS? The SART showed a low correlation with the ESS in both groups, which might be seen as evidence that both tests are sensitive to different features, ie, vigilance and sleepiness. However, there was no correlation between MSLT and ESS results either, which is surprising, as these tests are both thought to reflect sleepiness. This corroborates earlier reports of low or absent correlation between ESS and MSLT in narcolepsy; in fact, correlations are only moderate in controls.[9,12,20,23-26] Apparently, subjective assessment of sleepiness and a latency measure reflect significantly different aspects of sleepiness.

As for the diagnostic use of the SART, several remarks need to be made. Firstly, the new International Classification of Sleep Disorders-2 allows narcolepsy to be diagnosed by establishing a lack of hypocretin in the cerebrospinal fluid or by performing an MSLT.[21] This new approach will remove the need to perform an MSLT in a number of cases, particularly in those with cataplexy. In such cases, an assessment of impaired vigilance as a functional indicator of the severity of narcolepsy may be of use. Secondly, we compared narcoleptic patients with healthy controls, which explains the excellent sensitivity, specificity, and ROC of the SART and the MSLT. The contrast in results between groups is very likely to be less pronounced in a comparison with patients suffering from other disorders that also cause impaired vigilance. At present, we therefore do not advocate

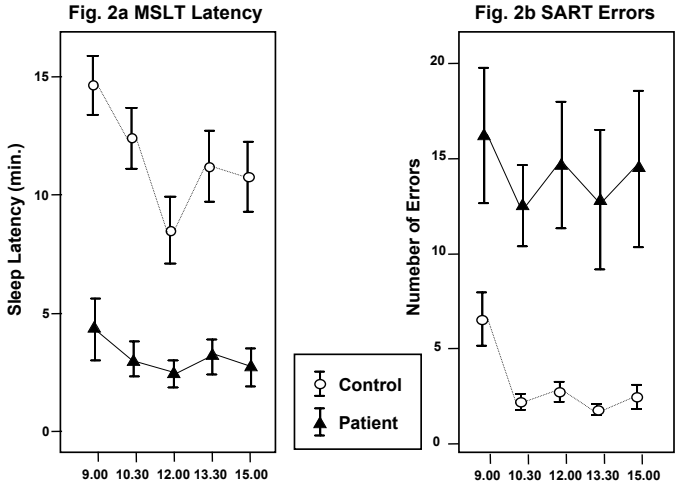

Figure 7.2
Diurnal effects
Multiple Sleep Latency Test (MSLT) latency (a) and Sustained Attention to Response Task (SART) error score (b) over the day. The MSLT latency and SART error score significantly differed between testing times in the control group. Error bars indicate SEM.

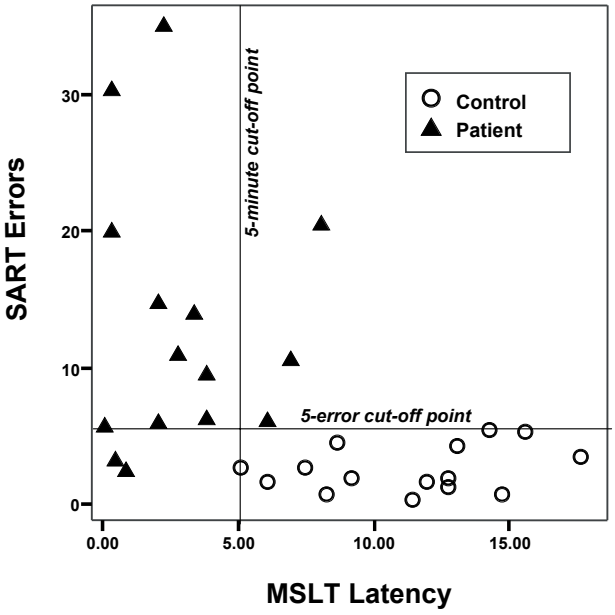

Figure 7.3
Correlation
Correlation between Sustained Attention to Response Task (SART) error score and Multiple Sleep Latency Test (MSLT) sleep latency. Circles represent controls, triangles represent patients. In the figure, the 5-error cutoff point of the SART and the 5-minute cutoff point of the MSLT are indicated by a line. There was no significant correlation between SART error score and MSLT sleep latency.

using the SART to distinguish between such disorders causing sleepiness; we contend that it is of use to measure vigilance.

There were diurnal effects on SART performance and MSLT latency. In controls, the noon MSLT latency was shorter than that of earlier MSLT periods, as has been found in earlier studies.[27-29] This effect was not significant in patients. In controls, the 9:00AM SART error score was significantly higher than that of other times. A possible explanation is that this reflects a brief learning effect, not fully covered by the 30-second introductory session. Another cause could be a diurnal effect. This effect meant that SART error scores of patients and controls were closer together at 9:00 AM than at other times, but there was still a clear difference at this time as well (Figure 7.2b).

Conclusion

The inability to remain vigilant during the day may be the most serious complaint in narcolepsy, since it impairs performance. The SART quantifies this neglected aspect and is valid, easy to administer, and takes little time to perform. Further studies are needed to probe the ability of the SART to measure treatment effects.

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