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Original Article

Disease-specific attention impairment in disorders of chronic excessive daytime sleepiness

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ABSTRACT

Objective: Patients with chronic excessive daytime sleepiness (EDS) complain of substantial attention deficits. However, their underlying neuronal dysfunction is largely unknown. Previous studies showed similar attention performances in central disorders of hypersomnolence suggesting that EDS-related cognitive impairment is independent of its cause. The aim of the current study was to further explore attentional profiles in disorders of chronic EDS.

Methods: Ten patients with narcolepsy type 1 (NT1; age 26.7 ± 9.3 years), 14 patients with idiopathic hypersomnia (IH; age 26.7 ± 9.3 years), 14 patients with subjective EDS (sEDS; age 31.4 ± 14.3 years), ie, a mean sleep latency >8 min in the multiple sleep latency test (MSLT), and 20 healthy controls (HC; age 32.6 ± 11.3 years) performed the vigilance task and the selective attention task of the test battery SLEEP® (Vienna Test System Neuro®). We assessed mean response time (RT) and standard deviation of RT separately for the first and the second half of the vigilance task to evaluate performance changes over time (time on task effect; TOT).

Results: A significant interaction effect between group and TOT on the mean RT in the vigilance task suggests partly group-specific attention deficits. Combining paradigms of sustained and selective attention discriminated patients with NT1, IH, sEDS and HC. Behavioral results were unrelated to the mean sleep latency in the MSLT.

Conclusions: Discriminative performance of the sustained and selective attention tasks indicate disease-specific components of attention in NT1, IH, and sEDS. Different temporal dynamics of attentional control efficiency might be one factor underlying group differences.

1. Introduction

The test battery SLEEP® (Vienna Test System Neuro®, Schuhfried GmbH, Mödling, Austria) was been developed to assess the fitness to drive in patients with sleep disorders and chronic excessive daytime sleepiness (EDS). It contains a selection of six paradigms to measure those aspects of attention that are expected to decline as a result of chronic EDS and that are also a necessary for intact driving performance (ie, tonic alertness, phasic alertness, vigilance, selective attention, divided attention and sustained attention) [1].

In a previous study, SLEEP®, in particular the paradigms for selective attention and vigilance, has been shown to be most sensitive to sleepiness-related cognitive decline in patients with central disorders of hypersomnolence [2]. However, the specificity of the attention profiles in patients with chronic EDS derived from SLEEP® have not yet been analyzed in detail.

The human attention system can be best subdivided into two domains, one representing the intensity aspect (ie, alertness and sustained attention), the other refers to the phasic aspects (ie, selective and divided attention) [3–5]. In its basic meaning, tonic alertness comprises the general level of response readiness as it is assessed in simple reaction-time tasks [6]. Moreover, tonic alertness also comprises a sustained function (ie, vigilance) [7] or sustained attention [8], describing a mentally effortful, self-initiated (rather than externally driven) preparedness to process and to respond. The ability to sustain tonic alertness under monotonous

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stimulus conditions – henceforth called sustained attention – is presumably related to a cingulo-opercular attentional control network which mediates widespread inhibition of neuronal activity to maintain cognitive resources available for current processing requirements [9–11].

Sustained attention is assessed by vigilance tasks such as the vigilance subtest of SLEEP®. This paradigm evaluates the ability to respond to rarely and irregularly occurring low-intensity discriminative stimuli. In sustained attention tasks, the performance progressively declines over time, a phenomenon which is known as the time on task (TOT) effect or the vigilance decrement [7].

Sustained attention, an endogenously maintained type of top-down attentional control, is distinguished from phasic aspects of attentional control such as selective attention [6,12]. Goal-directed behavior crucially relies on the ability to direct attention towards task-relevant information while ignoring irrelevant stimuli. The neurobiological substrate for top-down control of sensory processing involves a dorsal attention network (DAT) [13,14]. The selective attention paradigm of SLEEP® tests the ability to respond to predefined visual stimuli and to ignore other visual stimulus conditions.

Patients with a central disorder of hypersomnolence according to The International Classification of Sleep Disorders, third edition (ICSD-3) [15] report a range of cognitive, psychological and functional problems during daily life conditions [16]. Attention deficits are among the most frequently reported symptoms [16,17]. Narcolepsy refers to a syndrome with chronic EDS as the main symptom and cataplexies, sleep-related hallucinations and sleep paralysis as facultative symptoms. The pathophysiology of narcolepsy type 1 (NT1) is strongly associated with hypocretin deficiency, defined by cerebrospinal fluid (CSF) hypocretin 1 < 110 pg/mL. Mean sleep latencies in the multiple sleep latency test (MSLT) are below 8 min, in most cases below 5 min [18], accompanied by at least two sleep-onset rapid eye movement (REM) periods. Early studies on attention in patients with narcolepsy found performance impairment predominantly in long and monotonous tasks [19–21], whereas performance in short tasks with high cognitive demands was intact [20,22]. These results indicated that information processing might not be impaired on a functional but on a temporal level with progressive decline and increased variability of performance over time [20,21]. Later studies identified generally slower and more variable reaction times in all attention tasks, but deficits were pronounced in the more complex divided and flexible attention tasks [23]. It has been argued that these deficits result from a reduced availability of cognitive processing resources because patients need to constantly monitor vigilance state [24]. A recent study using a working memory paradigm concluded that impairment in patients with narcolepsy results from sustained attention dysregulation [25]. In sum, evidence points towards deficits in a wide range of attention paradigms. However, it remains unclear whether this deficit results from an inability to sustain cognitive function or whether it reflects a specific cognitive dysfunction beyond the temporal level, possibly related to disease pathophysiology itself.

Idiopathic hypersomnia (IH) is a rare central disorder of hypersomnolence which is characterized by chronic EDS, normal CSF hypocretin levels, a mean sleep latency below 8 min (mean 6.2 ± 3.0) and less than two sleep-onset REM periods in the MSLT [18]. In this condition, hypocretin 1 is not involved in the pathophysiology of chronic EDS and attentional deficits [26,27]. Instead, changes in histamine, GABA and dopamine neurotransmission as well as a dysfunction of the default mode network (DMN) have been suggested to play a role in the pathophysiology of IH [28]. Attention deficits in patients with IH were observed in studies that compared central disorders of hypersomnolence (ie, narcolepsy, IH and insufficient sleep syndrome). These studies used either the Sustained Attention to Response Task (SART), a 4-min go/no-go task, or the Psychomotor Vigilance Task (PVT), a 10-min simple reaction time task with a high rate of visual stimuli. The outcome measures did not reveal performance differences between the patient groups, which might disagree with the suggestion of a disease-specific component of attention dysfunction [29,30].

There is a neglected group of patients suffering from chronic EDS who score >10 on the Epworth Sleepiness Scale (ESS) but do not meet the diagnostic criteria for a disorder of hypersomnolence [1]. In this group, a mean sleep latency >8 min in the MSLT suggests a lower propensity to fall asleep in the daytime and better cognitive performance might be expected. These patients have not yet been studied with attention paradigms. We named this group subjective EDS (sEDS).

Whereas either the PVT or the SART have been used to compare disorders of hypersomnolence [29,30], there is no published study in which both intensity and selective aspects of attention were assessed by separate tasks. Thus, the aim of the current study was to explore whether patients with NT1, IH, and sEDS differ in their attentional profiles; ie, in performances of sustained attention and selective attention as assessed by the vigilance and selective paradigms of SLEEP®.

2. Methods

2.1. Subjects

We recruited 38 patients with suspected central disorder of hypersomnolence and 20 healthy control (HC) subjects. The inclusion criterion was an ESS >10. Patients with medication or substance use, a history of depression, insufficient sleep syndrome, a sleep-related breathing or movement disorder and other comorbid diseases associated with sleepiness were excluded. After comprehensive assessment, including detailed history-taking, polysomnography and MSLT, 10 patients were diagnosed as NT1, 14 as IH and 14 as sEDS; that is, patients that did not fulfill the criteria of a central disorder of hypersomnolence according to ICSD-3 [1].

2.2. Structured psychometric scales

To assess daytime sleepiness the ESS [31] was administered. The maximum ESS score is 24 (EDS), an ESS score >10 represents increased daytime sleepiness. In addition, the Fatigue Severity Scale (FSS) [32] was administered. It has a maximum mean FSS score of seven (normal range 2.3 ± 0.7). For the evaluation of the severity of a depressive syndrome we used the Beck Depression Inventory (BDI) [33]. BDI scores >13 indicate a depressive syndrome. Additionally, the habitual sleep duration, as assessed by the Pittsburg Sleep Quality Index (PSQI) [34], was used to identify patients with insufficient sleep syndrome and patients with long sleep duration (≥11 h).

2.3. Attention paradigms

An adapted version of the computerized test battery SLEEP® was applied. It contains subtests for tonic alertness, phasic alertness, vigilance, selective attention, divided attention and sustained attention. Similar attention tests of the Vienna Test System have been used in previous studies for the assessment of cognition in patients with narcolepsy and obstructive sleep apnea [35,36]. It has been shown that a vigilance paradigm similar to the vigilance task used in this study is sensitive to partial sleep deprivation [37].

Subjects performed the tasks during one session in a predefined order. The total duration of the test battery was 90 min; at half-time

participants had a break. The test battery was performed the day before the first polysomnograph, between 09:00 h and 13:00 h.

The most influential theories of the human attention system only distinguish intensity and selective aspects of attention on the neuronal level. A previous study showed that the subtests for vigilance (intensity aspect) and selective attention (selective aspect) were the most informative in patients with central disorders of hypersomnolence [2]. Thus, for the investigation of attention profiles we restricted our analysis to these clearly distinct attention functions as assessed by the corresponding SLEEP® paradigms for vigilance and selective attention.

2.3.1. Vigilance task (WAFV)

The paradigm of vigilance task (namely Perception and Attention Functions test battery – Vigilance; WAFV) refers to the definition of vigilance introduced by Mackworth et al. [7]. According to this view, the term 'vigilance' describes the ability to respond to rarely and irregularly occurring low-intensity discriminative stimuli. During the task, the participant had to respond to an intensity change in the color of a black square. During a task duration of 30 min, 900 stimuli were presented, discriminative stimuli were presented at a rate of 5% and in a predefined order. Mean response time (RT), the dispersion of RTs (standard deviation, SD) and the number of errors and omissions were calculated for the first and the second test half separately. The number of discriminative stimuli was identical between the first and the second halves of the test. The reliability of the mean RT was reported to be 0.96 (Cronbach's α) [38].

2.3.2. Selective attention task (WAFS)

Selective attention describes the ability to respond to a task-relevant stimulus while suppressing responses to irrelevant stimuli. In other words, intact performance in a selective attention task relies on the ability to prioritize specific stimuli in visual information processing. In the paradigm used here, various geometric stimuli (circle, square and triangle) were presented to the participant. The subjects responded to predefined stimulus conditions (intensity change of the circle or the square) while ignoring other stimulus conditions (no intensity change of circle, square or triangle, triangle intensity change). During a test duration of about 8 min, 144 visual stimuli were presented; a response is expected on 30 stimuli. The reliability of the mean RT is 0.95 (Cronbach's α) [49].

2.4. Statistical analysis

Primary outcome measures of attention tasks were the mean and SD of RT. RT data of each paradigm were inspected for extreme values. We identified one extreme value (mean RT of WAFS) which probably resulted from misunderstanding the instructions. Another two extreme values were found (mean RT of WAFV) which were interpreted as falling asleep. These scores were excluded from the analysis. In the next step, we performed logarithmic transformation in some variables that did not meet assumptions such as normal distribution or homogeneity of variances.

In the WAFS only were correct responses included in the RT analysis. In the WAFV, we analyzed RT measures twice, with lapses excluded and included (lapses were defined as responses not registered within 1 s after stimulus presentation). As the RT measures (excluding lapses) and the number of omissions showed high positive correlations (lowest: $r = 0.5$) it is reasonable to include lapses in the RT measures.

First, the statistical analyses were carried out with IBM SPSS® Statistics Software (version 25.0, IBM, Armonk, NY, USA). As we were specifically interested in group-specific performance changes over time, during the WAFV we performed repeated-measures analyses of covariance (ANCOVAs) for mean RT (log-transformed) and SD of RT with age, gender, and educational level as covariates. Second, a multivariate analysis of covariance (MANCOVA) was conducted to analyze group differences in the WAFS performance. Lastly, another MANCOVA was performed to investigate group discrimination by combining sustained and selective attention parameters. We included log-transformed mean RT and SD (WAFS) and measures of performance decline in the WAFV; ie, difference score between performance of the first and second test half, for mean RT (log-transformed; lapses included) and SD of RT. Age, gender, and educational level were included as covariates in all models. All (transformed) RT measures met the assumptions of the general linear model (including homogeneity of variance–covariance matrices).

Additionally, the number of omissions and the number of errors were analyzed for both tasks. As all transformations failed, we performed non-parametric statistical analyses such as the Kruskal–Wallis test and the Wilcoxon's test for between- and within-subject comparisons, respectively.

For statistical analysis of relations between measures we used Pearson's correlations in case of bivariate distribution of normality, otherwise Spearman's rank correlations were used. For all statistical analyses p was set at 0.05. p-Values were Bonferroni-adjusted for multiple comparisons.

3. Results

3.1. Subjects

Sociodemographic and psychometric data are presented in Table 1. Groups did not differ according to age ($H_{(3)} = 3.88$; $p = 0.28$) and gender ($\chi^2_{(3)} = 2.08$; $p = 0.56$). The educational level differed between groups ($H_{(3)} = 9.88$; $p = 0.02$), post hoc analyses revealed that patients with NT1 had a lower educational level compared to controls ($p = 0.02$).

Patients described increased self-reported sleep propensity as reflected by the ESS [31] ($H_{(3)} = 35.86$; $p < 0.001$). As expected patient groups presented similar subjective EDS. Moreover, all patient groups had fatigue scores (as assessed by the FSS [32]) above the normal range, however the FSS score did not differ between patient groups ($H_{(2)} = 0.79$; $p = 0.67$). Moreover, in NT1 and sEDS more than half of the patients complained at least a mild depressive syndrome as assessed by the BDI [33], while the frequency of a depressive syndrome did not significantly differ between patient groups ($\chi^2_{(2)} = 4.07$; $p = 0.13$). Self-reported habitual sleep time in the PSQI [34] did not differ between patient groups ($H_{(2)} = 1.26$; $p = 0.53$). Between 14% (IH, sEDS) and 20% (NT1) of the patients suffered from impairment in daily functioning that prevented them from having a steady job. About 40–57% of the patient sample had a relationship or family.

As expected, patient groups did not differ in any of the polysomnographic measures of the first night sleep (Table 2). Mean sleep latency in the MSLT of the sEDS-group was in the range of normal subjects; ie, 10.4 ± 4.3, and thus higher compared to patients with NT1 ($p < 0.001$) and patients with IH ($p = 0.001$). Mean sleep latencies were increased in the IH sample compared to NT1 but this was not statistically significant ($p = 0.36$). Ninety percent of patients with NT1 reached the lower threshold of 5 min in the MSLT which is more specific for narcolepsy [18]. In contrast, only 42% of the IH patients fulfilled this criterion.

Moreover, all patients with NT1 had cataplexies, which are specific for the diagnosis of narcolepsy. In addition, 50% of the NT1 patients had pathological CSF hypocretin 1 levels (10% had normal CSF hypocretin level, 40% had no available data). For patients with IH, CSF hypocretin levels were not available. In all IH patients the

Table 1
Subject characteristics.

	NT1 ($N = 10$)	IH ($N = 14$)	sEDS ($N = 14$)	Controls ($N = 20$)
Demographics				
Age	26.7 [20.0–33.4]	33.6 [26.8–40.4]	31.4 [23.1–39.7]	32.6 [27.3–37.9]
Gender (female/male)	3/7	11/3	12/2	13/7
Educational level	3.0 [2.4–3.6]	3.4 [2.9–3.9]	3.7 [3.1–4.3]	4.1 [3.7–4.5]
Psychometric data				
ESS	18.4 [10.5–20.3]	15.2 [11.9–18.5]	14.6 [13.4–15.8]	4.8 [3.4–6.2]
FSS	5.6 [4.9–6.3]	5.0 [4.2–5.8]	5.7 [5.2–6.2]	–
Habitual sleep time (PSQI)	7.6 [6.5–8.7]	7.6 [7.0–8.2]	8.0 [7.4–8.6]	–
Prevalence of depressive syndrome[a]	5 (62.5%[b])	2 (22.2%[b])	6 (54%[b])	–

Data are expressed as mean [95% confidence interval]. ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; sEDS, subjective excessive daytime sleepiness; PSQI, Pittsburg Sleep Quality Index. Educational level: 1 = no education, 2 = secondary school; 3 = professional education; 4 = A level; 5 = university education.
[a] Measured by Beck Depression Inventory (BDI).
[b] Percentage of the patients with available BDI-scores.

Table 2
Mean and 95% confidence interval of polysomnographic and multiple sleep latency test data.

	NT1 ($N = 10$)		IH ($N = 14$)		sEDS ($N = 14$)		Statistics
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
MSLT	2.5	[1.3–3.6]	5.3	[4.1–6.5]	12.1	[10.3–13.9]	$H_{(2)} = 29.40$; $p < 0.001$[a]
TST (min)	408.5	[364.9–452.1]	410.9	[387.9–433.9]	411.9	[389.4–434.4]	$F_{(2,35)} = 0.02$; $p = 0.98$[b]
Sleep efficiency (%)	87.8	[87.8–93,4]	90.0	[85.2; 94.8]	87.8	[84.0–91.6]	$F_{(2,35)} = 0.38$; $p = 0.69$[b]
N1 (%)	5.9	[2.5; 9.3]	3.9	[2.5; 5.3]	4.2	[3.2; 5.2]	$F_{(2,18.28)} = 0.69$; $p = 0.52$[c]
N2 (%)	44.9	[36.8–53.0]	46.5	[42.4–50.6]	43.8	[40.0–47.6]	$F_{(2,35)} = 0.38$; $p = 0.69$[b]
N3 (%)	20.3	[14.7–25.9]	23.4	[18.8–28.0]	24.3	[20.5–28.1]	$F_{(2,35)} = 0.82$; $p = 0.45$[b]
REM (%)	17.8	[13.9–21.7]	18.1	[14.1–22.1]	20.0	[16.5–23.5]	$F_{(2,35)} = 0.49$; $p = 0.62$[b]
WASO (min)	49.2	[26.4–72.0]	40.9	[16.0–65.8]	31.1	[17.1–45.1]	$F_{(2,35)} = 0.84$; $p = 0.44$[b]
AHI	3.8	[0.2–7.4]	2.3	[−0.2–4.8]	1.0	[0.0–2.0]	$F_{(2,16.93)} = 1.56$; $p = 0.24$[c]
ODI	3.5	[0.1–6.9]	1.4	[−0.3–3.1]	0.8	[0.0–1.6]	$F_{(2,17)} = 1.58$; $p = 0.23$[c]
PLM	14.7	[−3.3–32.7]	7.9	[1.1–14.7]	5.1	[−0.3–10.5]	$F_{(2,18.57)} = 0.77$; $p = 0.48$[c]

AHI, sum of apneas and hypopneas per hour; CI, confidence interval; IH, idiopathic hypersomnia; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; ODI, desaturation events per hour; PLM, periodic leg movements per hour (index); REM, rapid eye movement; sEDS, subjective excessive daytime sleepiness; TST, total sleep time; WASO, wake time after sleep onset.
[a] Kruskal–Wallis H-test.
[b] One-way analysis of variance.
[c] Welch's F-test.

clinical syndrome missed facultative narcolepsy symptoms and no sleep-onset REM periods during the MSLT naps were observed. Patients with sEDS were distinguished from the IH-group only by a mean sleep latency within the normal range.

3.2. Behavioral data

3.2.1. TOT effect in the vigilance task

The performance data of the WAFV are presented in Fig. 1. A repeated-measures ANCOVA revealed that log-transformed mean RT (lapses excluded) significantly decreased in the second half of the task ($F_{(1, 49)} = 4.8$, $p = 0.03$). Whereas groups differed in the mean RT ($F_{(3, 49)} = 5.1$, $p = 0.004$) we found no significant interaction between TOT and group ($F_{(3, 49)} = 0.4$, $p = 0.75$) or any of the covariates. However, the interaction between TOT and group became significant for mean RT when including lapses ($F_{(3, 49)} = 3.6$, $p = 0.02$) indicating that the number of lapses plays an important role in the discrimination between groups.

SD of RT did not change between the first and the second halves of the test ($F_{(1, 49)} = 0.5$, $p = 0.50$) but we found a significant group effect ($F_{(3, 49)} = 4.3$, $p = 0.009$). The TOT effect did not differ between groups ($F_{(3, 49)} = 0.9$, $p = 0.46$). Moreover, covariates did not have a significant effect on the SD of RT. The results did not change when lapses were included.

The rate of omissions ($H = 16.8$; $p = 0.001$) as well as the number of committed errors ($H = 24.2$; $p < 0.001$) differed between groups in the first half of the WAFV. Pairwise comparisons revealed a higher number of omissions and errors in patients with NT1 ($p = 0.001$; $p < 0.001$) and in patients with sEDS ($p < 0.04$; $p = 0.001$) but not in patients with IH ($p = 0.06$; $p = 0.09$) compared to controls. During the second half of the WAFV all patient groups reached significant higher scores of omissions ($H = 21.7$; $p < 0.001$) compared to controls. Patients with NT1 ($p = 0.01$) and sEDS ($p = 0.001$) had increased error rates in the second half of the WAFV. The performance decline from the first to the second part of the task differed between groups. Whereas patients with IH ($W = 42.5$; $p = 0.017$) showed a significant increase and patients with NT1 ($W = 39.0$; $p = 0.05$) an almost significant increase of omission rate, for the other patient groups omission rates did not significantly change over time (sEDS: $W = 41$; $p = 0.47$; HC: $W = 17.5$; $p = 0.53$).

In sum, mean RT (including lapses) and omission rate showed evidence for a group-specific TOT effect.

3.2.2. Selective attention performances

WAFS data are shown in Fig. 2. A MANCOVA yielded group differences across the primary WAFS outcome measures: mean RT (log-transformed) and SD of RT (Pillai's Trace; $V = 0.37$, $F_{(6, 96)} = 3.7$, $p = 0.003$). Moreover, age showed a significant effect on the outcome measures (Pillai's Trace; $V = 0.19$, $F_{(2, 47)} = 5.5$, $p = 0.007$).

Compared to controls the number of omissions was increased in patients with sEDS ($H = -14.38$; $p = 0.016$), whereas in patients with NT1 the increase was not significant ($H = -12.58$; $p = 0.09$). Patients with IH even had a normal score of lapses ($H = -1.59$; $p = 1.00$). The number of errors also increased in patients with sEDS ($H = -24.1$; $p < 0.001$) and in patients with NT1 ($H = -17.6$;

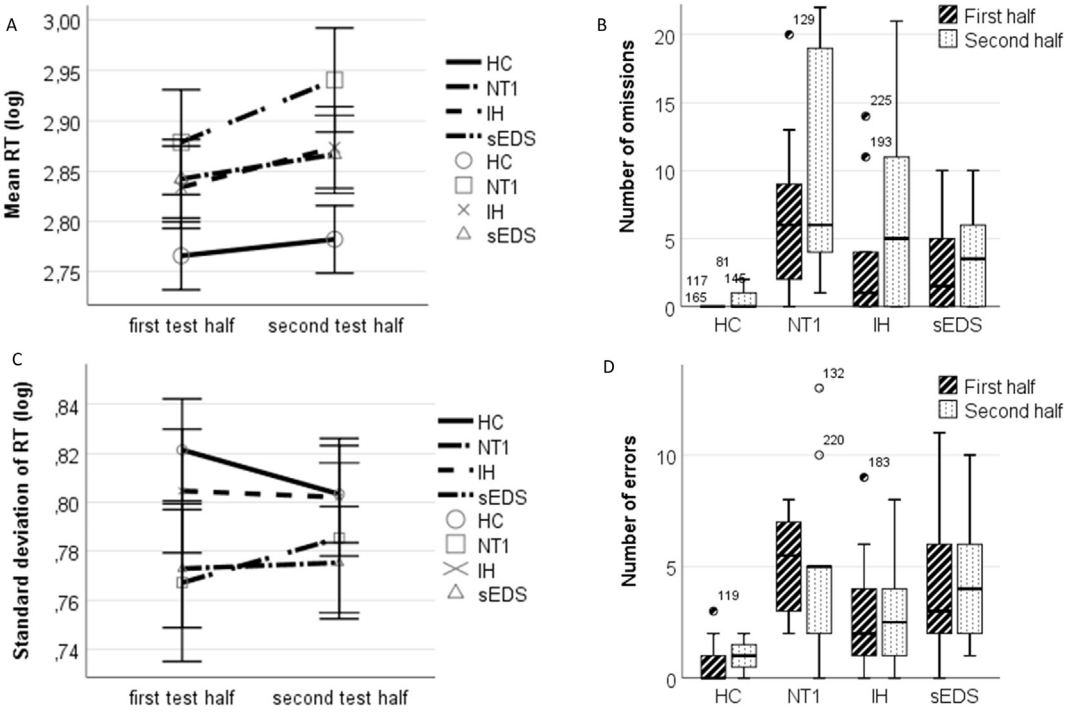

Fig. 1. Sustained attention performances in the vigilance task. HC, healthy controls; NT1, Narcolepsy type 1; IH, Idiopathic Hypersomnia; sEDS, subjective excessive daytime sleepiness. Performances are separated into the first and the second test half. 1A. Mean of log-transformed response times (including lapses). 1B. Median and quartiles of the number of omissions. 1C. Mean of RT dispersion (log-transformed standard deviation). 1D. Median and quartiles of the number of errors. Error bars represent the 95% confidence interval.

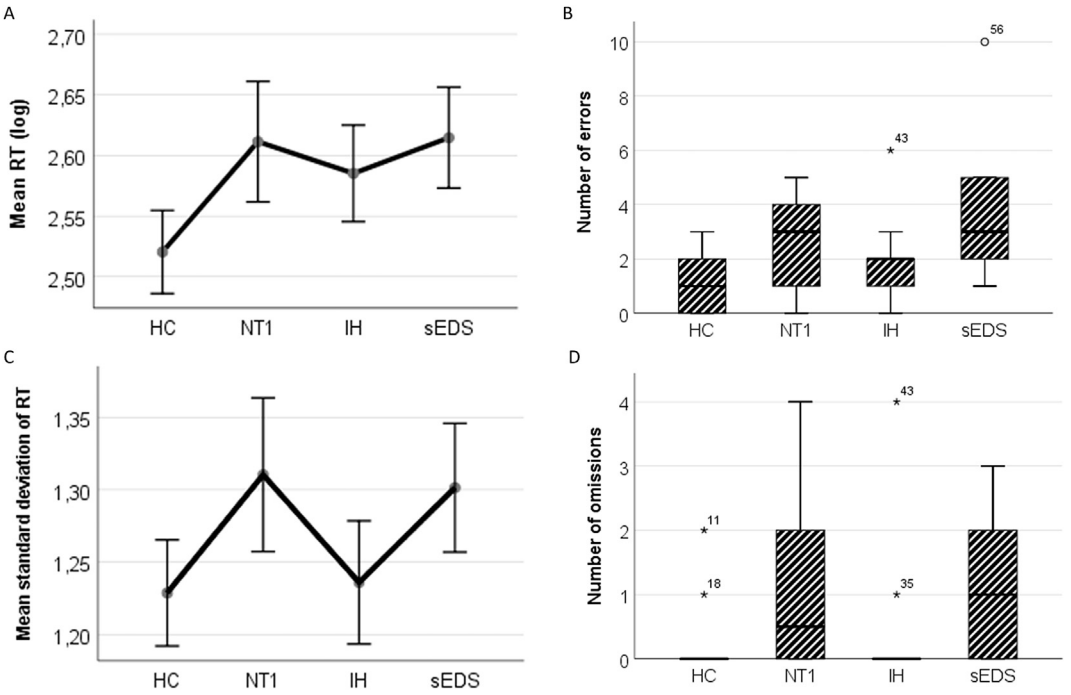

Fig. 2. Selective attention performances for each group. HC, healthy controls; NT1, Narcolepsy type 1; IH, Idiopathic Hypersomnia; sEDS, subjective excessive daytime sleepiness. 2A. Mean of log-transformed response times. 2B. Median and quartiles of the number of errors. 2C. Mean of RT dispersion (log-transformed standard deviation). 2D. Median and quartiles of the number of omissions. Error bars represent the 95% confidence interval.

$p = 0.03$) compared to controls, but in patients with IH it did not differ from healthy subjects (H = −9.0; $p = 0.67$).

In sum, mean RT, SD of RT as well as error and omission rates of the WAFS may be helpful in the discrimination of patients with central disorders of hypersomnolence.

3.2.3. Group discrimination combining sustained and selective attention performances

A MANCOVA revealed that the groups significantly differed across the four main outcome measures of both attention tasks (Pillai's Trace; V = 0.57, $F_{(12, 141)} = 2.8$, $p = 0.002$). WAFS mean RT

and SD of RT (both with lapses excluded), and WAVF difference score for mean RT and SD of RT (lapses included). Moreover, age (Pillai's Trace; V = 0.22, $F_{(4\ 45)} = 3.1$, $p = 0.024$) and gender (Pillai's Trace; V = 0.19, $F_{(4\ 45)} = 2.6$, $p < 0.05$) affected the outcome measures.

The MANCOVA was followed by a discriminant function analysis, which revealed three discriminant functions. The first explained 74.1% of the variance (canonical $R^2 = 0.47$), the second explained 14.6% (canonical $R^2 = 0.15$) and the last 11.2% (canonical $R^2 = 0.12$). In combination, the three variates significantly differentiated the groups ($\lambda = 0.4$; $\chi^2_{(12)} = 45.8$; $p < 0.001$). Combining the second and the third variate also discriminated groups ($\lambda = 0.8$; $\chi^2_{(6)} = 14.3$; $p = 0.027$) as well as the third variate alone ($\lambda = 0.9$; $\chi^2_{(2)} = 6.3$; $p < 0.044$). WAF mean RT difference loaded highly on the variates 2 ($r = -0.69$) and 1 ($r = 0.68$) but was not related to variate 3 ($r = 0.07$). WAFV difference of RT SD showed mild correlations with all variates (highest $r = 0.15$). WAFS mean RT was strongly related to variate 2 ($r = 0.64$) and variate 1 ($r = 0.58$), moderately to variate 3 ($r = -0.45$). WAFS SD of RT loaded highly on variate 3 ($r = 0.80$) and variate 1 ($r = 0.52$) and moderately on variate 2 ($r = 0.32$).

The discriminant function plot (Fig. 3) shows that the first function discriminated HC from the patient groups (best possible from the NT1-group) by a factor that affects the performance decline in the WAFV (mean RT difference) as well as the selective attention performance. The second function differentiated patients with sEDS from the other groups (best possible from the NT1-group) by an underlying dimension that affects the WAFV mean RT difference and the performance in the WAFS in the opposite direction. Thus, contradicting performance in the WAFV (ie low TOT effect) and in the WAFS (ie performance deficit) helps to differentiate sEDS from NT1 and IH. The third function discriminated patients with IH from the other groups (best possible from the NT1-group) by a factor that affects the WAFS mean RT and SD of RT in opposite directions. Thus, a decreased WAFS mean RT in combination with a preserved WAFS SD of RT helps to distinguish IH from the NT1 and sEDS.

Based on the four main outcome measures of WAFV and WAFS 75% of the HC, 66.7% of patients with NT1, 46.2% of the IH-group and 46.2% of the sEDS-group were correctly classified. Classification accuracy may be further improved when integrating error and omission scores.

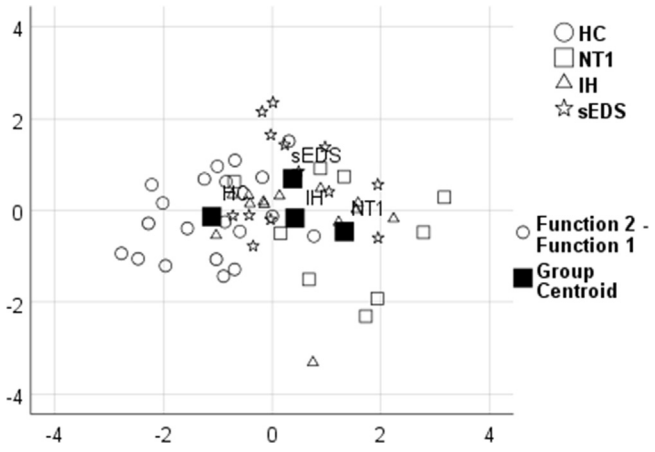

Fig. 3. Canonical Discriminant Functions. Unstandardized variate scores for each subject. Group centroids represent the mean variate score for each group. HC, healthy controls; NT1, Narcolepsy type 1; 1H, Idiopathic Hypersomnia; sEDS, subjective excessive daytime sleepiness.

3.3. Correlations between attention performances and other measures

Regarding the WAFV, a higher ESS score was related to a higher mean RT (log-transformed; including lapses) in the first test half ($r = 0.56$; $p < 0.001$) and in the second test half ($r = 0.69$; $p < 0.001$). Furthermore, the ESS score was positively related to the number of omissions in the first half ($r = 0.51$; $p < 0.001$) and the second half ($r = 0.58$; $p < 0.001$), and the error rates of the first half ($r = 0.55$; $p < 0.001$) and second half ($r = 0.33$; $p < 0.02$) of the task. Mean sleep latency in the MSLT did not correlate with any of the WAFV outcome measures.

Regarding the selective attention test, ESS score showed statistically significant but moderate correlations with log-transformed mean RT ($r = 0.41$; $p = 0.002$), the SD of RT ($r = 0.32$; $p < 0.02$), the number of omissions ($r = 0.35$; $p = 0.01$) and the number of errors ($r = 0.39$; $p = 0.04$). Selective attention test performance was not correlated with mean sleep latency in the MSLT.

In our sample ESS score and mean sleep latency in the MSLT were not related ($r = -0.18$; $p = 0.28$).

4. Discussion

The aim of the current study was to further explore attentional profiles in central disorders of hypersomnolence. Taken together, combining outcome measures of the sustained and selective attention paradigms helps to discriminate NT1, IH and sEDS. Moreover, performance measures were not related to sleep propensity as measured by the MSLT. This might imply that attention impairment also involves disease-specific components beyond the common EDS-related cognitive decline.

Two previous studies compared cognitive performance between patients with different central disorders of hypersomnolence. In one study no differences in the PVT were found between NT1 and IH patients [30]. The other study compared patients with narcolepsy, IH and obstructive sleep apnoea syndrome regarding their performance in the SART [29]. They did not find differences and concluded that cognitive impairment is related to chronic EDS irrespective of its cause. In our study, we identified a linear combination of performance measures that discriminated groups by their severity of attention impairment in general, with NT1 severely impaired and sEDS showing the lowest impairment. But beyond that we found combinations of specific variables that were negatively related highlighting that group-specific characteristics might exist that cannot be related to one underlying factor (ie, severity of daytime sleepiness). The findings that patients with NT1 and IH neither differed in the ESS score nor in the mean sleep latency (MSLT) and attention performance was not related to the mean sleep latency in the MSLT supports our interpretation.

A pronounced TOT effect in the WAFV in combination with a low selective attention performance; that is, increased mean RT, SD of RT, errors and omissions, was indicative of the NT1-group. The performance deterioration within the first 15 minutes of the vigilance task is in agreement with previous study findings in patients with narcolepsy [23]. However, the deficit in the selective attention task contradicts earlier studies that showed slowing of information processing but preserved quality of performance in tasks of selective attention [23,24]. We suggest that the different testing procedures account for the contradictory results since the previous studies used very short tasks of 3–5 min duration, whereas in our study the selective attention task lasted for 8 min. In sum, one might interpret the findings that patients with NT1 can preserve task performance during very short time intervals but show fluctuating and fast declining performance when test duration is extended and complex selective attention is required. This would

be in line with the finding that attention deficits become increasingly obvious in tasks that put high demands on attentional control processes because here information processing needs to be even more efficient [40]. Whereas in the selective attention task irrelevant stimuli must be inhibited, in the sustained attention test response readiness needs to be sustained when discriminative stimuli are rare.

Patients with IH were best discriminated from NT1 as they showed partly preserved selective attention performance, ie, WAFS mean RT increased but the SD of RT, errors and lapses were in the normal range. In addition, performances were generally better than in the NT1-group even though a pronounced TOT effect was present in the IH-group. The data might suggest that in patients with IH, attention performance cannot be intrinsically maintained over longer time periods and thus strongly depends on a stimulating environment. The finding of an increased TOT effect has already been shown in sleep-deprived subjects [41] indicating similar mechanisms in sleep-deprived subjects and IH. It has been suggested that a progressive performance decline in vigilance tasks might be related to sleep regulatory processes induced by the sustained use of neuronal networks facilitating task performance [41–43]. A theoretical account for the TOT effect in healthy subjects is the resource-control theory of sustained attention [44]. According to the theory, failures of executive control result in a disproportionate amount of attentional resources allocated to mind wandering so that resources for the primary task are reduced [45]. A decreasing executive control over time presumably results from the fact that subjects have learned to engage less in effortful information processing when a task is monotonous and not externally demanding [44]. We speculate that emotional–motivational interactions with sleep regulatory processes or directly with attentional control are among the potential causes for the disability to intrinsically sustain attention performance over a longer time period.

The sEDS-group was best discriminated from NT1 as they showed a discrepancy between a mild TOT effect and a more pronounced selective attention deficit. All things considered, patients with sEDS presented substantial fluctuations of task performance that are less dependent on task duration and task requirements, ie this performance pattern was observed in both tasks and changed less over time. Importantly, positive high correlations between RT and the number of omissions and errors (in both tasks) indicate that erroneous responses (lapses and errors) resulted from a comprised task processing (ie responses were longer due to decision uncertainty). In contrast, in healthy subjects attentional control tasks typically result in faster errors because of inappropriate action impulses [46,47]. The data in the sEDS-group might be interpreted as a rapidly fluctuating attentional control efficiency [9]. However the cause for this remains speculative. One possibility is an underlying subclinical atypical depressive syndrome which is difficult to detect by the BDI. The fundamental attention impairment in patients with sEDS would be congruent with the findings of widespread cognitive impairment in patients with non-melancholic atypical depressive disorder [48].

In our study the propensity to fall asleep in the daytime, as measured by the MSLT, did not represent subjective sleepiness as indexed by the ESS. However, recent studies showed significant correlations between MSLT and ESS in sleep disorders with hypersomnolence [49,50]. Our contradicting finding may be explained by the fact that we explored the correlation over all groups due to the small sample sizes. We suggest the relationship between MSLT and ESS to be affected by the sEDS-group. In contrast, better performance in the vigilance task correlated with a lower ESS but was not related to the mean sleep latency in the MSLT. Moreover, the sEDS group showed substantial cognitive impairment but a mean sleep latency >8 min in the MLST. Therefore, we conclude that sleep propensity should be regarded as only one aspect of chronic EDS, the quality of the state between fully awake and sleep is of similar importance for the understanding of the nature of disorders of chronic EDS.

Our study had several limitations that might have affected the reliability of our results. First, as this was an exploratory study we investigated rather small sample sizes of each patient group which may reduce the external validity of our results. In addition, high interindividual variation of the attentional performances within the groups, particularly in the sEDS-group, lead to moderate discrimination rates for some patient groups. This suggests that there are more factors that need to be taken into account to reliably discriminate groups. Future studies combining neuropsychological, neurophysiological and imaging methods might help to overcome these shortcomings.

5. Conclusion

In this exploratory study we provide initial evidence of slightly different attentional patterns in drug-free patients with NT1, IH and sEDS which are independent of daytime sleep propensity (MSLT). This study cautiously suggests that chronic EDS is not a unitary construct but should be divided into subtypes of chronic EDS. Our results emphasize the importance of investigating the quality of the wake state to further our understanding of disorders of chronic EDS. Distinct temporal dynamics of attentional control efficiency might be one factor underlying differences in the attentional performances, but this needs further investigation.

Conflicts of interest

M.B. has received speaker honoraria from UCB Pharma GmbH, Bioprojet GmbH, Sanofi-Genzyme GmbH and Sanofi-Genzyme Europe. A.J. received travel support from UCB and Inspire Medical Systems. A.H. received speaker honoraria from UCB Pharma GmbH, Bioprojet GmbH, Löwenstein Medical and travel support from Habel Medizintechnik and Vivisol Austria. P.Y. obtained speaker honoraria from Sanofi-Genzyme GmbH, Sanofi-Genzyme Europe, UCB, BioMarin, Neuro-Consil, Löwenstein Medical, Medice, Inspire, Vanda, Bayer Vital and Cortex. P.Y. received honoraria for advisory agreements from Genzyme GmbH, Sanofi-Genzyme Europe, BioMarin, Medice, Vanda and Inflectis. P.Y. declares that there is no conflict of interest concerning the contents of this specific paper. M.R. and N.L. have nothing to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.021.

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