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Cognitive impairment in fatigue and sleepiness associated conditions

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ABSTRACT

Although relating to very different concepts, sleepiness and fatigue are often confounded. However, both fatigue–associated conditions such as the chronic fatigue syndrome (CFS) and sleepiness–associated conditions such as the sleep apnea–hypopnea syndrome (SAHS) are associated with cognitive impairment with impaired attention, concentration and memory performances. Fifteen pure CFS patients, without primary sleep disorders or clinically relevant sleepiness, were compared to 15 untreated SAHS patients, without clinically relevant fatigue, and to 16 healthy controls of similar age. The auditory verbal learning test (AVLT), digit span, digit symbol and finger tapping test (FTT) were used as cognitive and behavioural measures. In addition we assessed daytime EEG spectral power and P300 evoked potentials. With exception for the digit span, all tests showed lower performances in patient groups. Recall on the AVLT did not differ between the two patient groups, but the digit and symbol spans showed more severe impairment in SAHS patients. Psychomotor performance on the FTT presented with slower hit rates in SAHS than in CFS. EEG theta power was highest in CFS patients. P300 latencies and amplitudes did not differ between groups. Fatigue– and sleepiness–associated conditions can both present with significant and objective impairment of cognitive functioning and behavioural motor performance. In our sample cognitive impairment and psychomotor performance were worse when associated to sleepiness in SAHS than with fatigue in CFS.

1. Introduction

Although relating to very different underlying concepts, fatigue and sleepiness are often difficult to distinguish for both clinicians and patients and continue to be often confounded (Pigeon et al., 2003). Whereas excessive daytime sleepiness (EDS) is mainly related to sleep propensity in general and to primary sleep disorders in particular (sleep apnea, periodic limb movement disorder, narcolepsy e.g.), chronic daytime fatigue is associated to a feeling of exhaustion, a lack of energy. By definition fatigue usually requires rest, not sleep, for recover. Therefore it is rather related to systemic conditions (auto-immune diseases, inflammatory or infectious states, and major depression) and insomnia (a hyper-arousal condition), and it is the core symptom of the chronic fatigue syndrome for instance (Pigeon et al., 2003; Shen et al., 2006; Neu et al., 2008). Both complaints (daytime fatigue and EDS) have nevertheless been related to total sleep deprivation (Shen et al., 2006). Chronic daytime fatigue and EDS have both been associated with reported impairments of concentration and short-term memory (Shen et al., 2006) and with affective symptoms (Neu et al., 2010).

A potential increase in the comprehension of both concepts might be mediated by investigations of associated aspects, such as cognitive impairment, in fatigue- and sleepiness-related clinical conditions.

Sleep apnea–hypopnea syndrome (SAHS) is a primary sleep disorder (PSD) that presents with EDS (Lavie, 2008; Roure et al., 2008; Pizza et al., 2009) and with cognitive impairment (Sateia, 2003; Antonelli et al., 2004; El-Ad and Lavie, 2005).

Verbal memory impairment and lowered performances on the Wechsler Adult Intelligence Scale WAIS digit or symbol span have already previously been reported in untreated SAHS patients (Décary et al., 2000; Bardwell et al., 2001; Verstraeten et al., 2004; Verstraeten, 2007). Continuous nasal positive airway pressure (nCPAP) has shown to improve cognitive dysfunction in SAHS patients (Bardwell et al., 2001; Ferini-Strambi et al., 2003).

Although that SAHS patients showed reduced eyes-closed EEG alpha power (Wong et al., 2006), other daytime waking EEG measures such as theta power did not differentiate sleepiness levels, in a group of nocturnal breathing disordered patients (e.g., NBDP as SAHS), with various degrees severity (Sforza et al., 2002). Previous studies of event-related potentials (ERP) investigating the P300 in SAHS patients have conflicting results, showing either increased latencies (Gosselin et al., 2006) or similar latencies to controls (Wong et al., 2006).

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Chronic fatigue syndrome (CFS) is a nosologically defined clinical entity presenting with severe and invalidating daytime fatigue (Maquet et al., 2006; Neu et al., 2007; Wyller, 2007). Altered short-term memory and attention disabilities have also been repeatedly reported in CFS (Michiels et al., 1996; Wearden and Appleby, 1997; Michiels and Cluydts, 2001; Capuron et al., 2006; Maquet et al., 2006). Lower performances on the finger tapping test (FTT), on the WAIS digit and symbol span subtests and impaired verbal learning memory in particular have been mentioned in these patients (Michiels et al., 1996). Cognitive Behavioural Therapy has shown to lead to an improvement in the perception of cognitive impairment but not on neuropsychological tests such as the symbol span (Knoop et al., 2007).

Electrophysiological investigation also showed also greater EEG theta power in a group of CFS patients during a simple motor task (Siemionow et al., 2004). Whether fatigue- and sleepiness-associated conditions, in appropriate selected groups, can reveal similar quantitative EEG findings has not yet been investigated. P300 ERPs from auditory stimuli did not reliably discriminate CFS from matched control subjects (Polich et al., 1995).

In a previous study we mentioned a possible significant complaint of sleepiness in a group of 'pure' (without any PSD or DSM-IV Axis I and II disorders) CFS patients compared to healthy controls (Neu et al., 2008). Therefore, we chose in the present study to compare cognitive function and psychomotor performance in SAHS patients (as a model of EDS) without clinically significant fatigue and in pure CFS patients (as a model of fatigue) without clinically significant EDS complaints with healthy control subjects.

We assessed cognitive function using the auditory verbal learning test (AVLT) and the WAIS digit and symbol spans and psychomotor performances with the finger tapping test (FTT). Affective symptoms and sleep quality perception were also recorded using the Hamilton depression (HAMD 21) and anxiety (HAMA) scales, the Beck depression inventory (BDI 13-items short form) and the Pittsburgh Sleep Quality Index (PSQI) respectively.

According to previous reports in the literature, regarding attention deficits and short-term memory complaints in both fatigue- and sleepiness-associated conditions as CFS and SAHS, we hypothesised that cognitive and behavioural functions, as measured by standard testing, would show similar results under these conditions when compared to healthy controls. Therefore the main objective of the present study was to compare the potential cognitive impairment profiles, assessing easy-to-use routine tasks of attention, memory and psychomotor performance parameters (FTT mean hit rates), in two patient groups, with an EDS complaint (SAHS patients) or a clinically significant fatigue complaint (CFS patients) respectively. Secondary and descriptive outcomes concerned FTT hit rate distribution and electrophysiological measures from waking EEG spectral power and event-related potentials (P300).

2. Methods

The present study was carried out in a population assigned to a general university hospital's sleep laboratory. Final inclusion of subjects was based on clinical selection criteria (see below) and the results of a full night polysomnographic recording.

2.1. Subjects

Patients were recruited using a cross-sectional design. First step selection criteria were identical to a previous study and described in detail elsewhere (Neu et al., 2008). From September 2006 to April 2007, patients exhibiting only CFS were referred to the sleep unit after a full medical check-up. Center for Disease Control criteria were used for the first selection of CFS patients (Fukuda et al., 1994); furthermore clinical criteria for narcolepsy or idiopathic hypersomnia and all DSM-IV axis 1 diagnoses were excluded. Final inclusion was only decided after a full night polysomnographic (PSG) recording in order to avoid overlaps with primary sleep disorders (Apnea–Hypopnea Index (AHI) and Periodic Limb Movement index (PLMi) had to be <5/h e.g.) in the CFS group and to set inclusion diagnosis in the SAHS group. SAHS patients were referred from the pneumonology department of the same hospital, for a clinically suspected nocturnal breathing disorder. The inclusion setting for SAHS patients was an AHI >15/h based on the PSG recording. Healthy Controls (HC) were locally-recruited healthy volunteers who received between 100 and 180 Euros from private funding at the end of the study. Regular Sleep–Wake schedules were required and no shift working was allowed. Control subjects had no significant somatic conditions and no current or past mental disorders. Further exclusion criteria were identical to those for the patients groups. In order to avoid gender mismatch, only female subjects were studied. All patients and subjects were free of any neuropsychopharmacological treatment (including pain medication) for at least two weeks prior to recording. Daytime napping was not allowed in the sleep unit. All patients in our lab completed questionnaires about lifestyle and drinking habits. Patients with a consumption of more than two units of alcohol per day were excluded. All patients and controls received a standard physical examination, structured clinical interview for DSM-IV (MINI, SCID-I) and psychometric assessment. All subjects were reportedly right-handed.

In a previous study we mentioned an unexpected overlap of possible sleepiness with fatigue in a sample of 'pure' CFS without PSD (Neu et al., 2008). In addition to the above-mentioned criteria, we therefore fixed the threshold on the Epworth Sleepiness Scale (ESS) at <10 for CFS patients in the present sample, as a supplementary inclusion criterion. Therewith we also fixed the threshold on the mean score of the Fatigue Severity Scale (FSS) score <4 for SAHS patients to avoid possible overlap of clinically relevant fatigue complaints. Finally 46 subjects (15 CFS patients, 15 SAHS patients and 16 HC) have been included in the present study, for further analyses as described below.

2.2. Procedure

All patients and control subjects stayed for three days (two nights) in our sleep lab. Neurocognitive testing was carried out during the second day after a full night PSG and electrophysiological measures were assessed on the third and last day after a second PSG recording. The minimum threshold of preceding recorded Total Sleep Time (TST) was 300 min for all subjects.

All patients and controls gave informed written consent and the study was conducted in accordance with the rules and regulations for clinical trials stated by the World Medical Assembly in Helsinki.

2.3. Material

2.3.1. Sleepiness and fatigue scales

The *Fatigue Severity Scale* (FSS) is a self-reporting tool used to assess levels of fatigue and its effect on daily functioning (Krupp et al., 1989). The FSS was introduced for individuals with multiple sclerosis and systemic lupus erythematosus (Krupp et al., 1989). In addition it has been used in many studies investigating fatigue in other chronic conditions like obesity, Parkinson disease, hepatitis C infection and also in CFS (Olson et al., 2003) and in general population samples (Lerdal et al., 2005; Stone et al., 2000). The FSS is a 9 item, 7-point Likert-type scale. Scores are usually reported as 'mean scores' (ranging from 1 to 7) obtained by dividing the total score (ranging from 7 to 63) by 9. The most often proposed cut-off point on mean scores is 4 (Flachenecker et al., 2002; Kos et al., 2007). Other authors have also proposed a cut-off of 5 (Lerdal et al., 2005).

The *Epworth Sleepiness Scale* (ESS) is one of the most widely used scales of subjective sleepiness. The ESS consists of 8 items (described situations) arranged on a 4-point Likert scale ranging from 0 ("never doze") to 3 ("high chance of dozing" during daytime). The summed scores range from 0 to 24 and scores above 10 are commonly interpreted as clinically relevant increased daytime sleepiness (Johns, 1991).

The *Pittsburgh Sleep Quality Index* (PSQI) assesses subjective sleep quality. The 19 items are grouped into seven component scores, each weighted equally on a scale from 0 to 3. These components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction. The component scores are then summed to yield the global PSQI score. In validation studies, a global PSQI score >5 indicates that a subject is having severe difficulties in at least two areas, or moderate difficulty in more than three areas (Buysse et al., 1989).

2.3.2. Neurocognitive, behavioural and neuropsychological testing

The *digit span* is a subtest of the WAIS (Wechsler, 1981). It requires that the examinees repeat verbatim or in reverse order, strings of digits recited at the rate of one per second. The length of the strings is gradually increased. Both conditions, digits forward and backward, were administered. The test was discontinued in each condition, according to the standard rule, after two failures of correct repetition. Forward digits were always presented before backwards digits. The correct repetitions in each condition and the overall total number of correct digits were recorded. In this test, digit repetition in forward condition tests for short memory capacity, whereas backward repetition of digits additionally probes the central executive component of working memory responsible for information updating and manipulation (Baddeley, 2001).

The *symbol span or Digit Symbol Substitution Test* (DSST) assesses sustained attention, speed of response, and visual scanning and is also a part of the WAIS (Wechsler, 1981). The DSST was stopped after 1 min and 30 s and the total number of correct digits was recorded.

The *Rey Auditory Verbal Learning Test* (AVLT, Rey, 1941) was used with the following procedure: a list (A), of 15 unrelated words, was read one at a the time by the examiner (DN) at a pace of one word per second. The examinee then had to recall all of

the words that she could remember. This procedure was repeated five times (trials A1 to A5). Subsequently, a second list (B), of 15 unrelated words, was read at the same pace as list A, and had to be recalled (interference list, B1). In the 6th trial, the original list had to be recalled once again without a preceding reading by the examiner (trial A6). After 20 min, a delayed recall trial (trial A7) was performed followed by a recognition task. The recognition list contained the 15 original words, the 15 words from the interference list and 20 semantically or phonologically related new words.

The finger tapping test (FTT) is considered a reliable indicator of execution motor speed (Halstead, 1947) and consisted here of five consecutive trials of 10 s with the index finger of each hand beginning with the right (dominant) hand. The number of taps for each trial and the mean number of taps were computed.

Cognitive testing was conducted between 10:30 a.m. and 12:00 p.m. on the second day of the hospitalisation after a first night of polysomnographic recording.

2.3.3. Affective symptoms scales

All patients completed the 13-item short form of the *Beck Depression Inventory* (BDI) on the first day of their stay in our laboratory before the first night of polysomnographic recording between 5 pm and 7 pm All subjects were rated with the *Hamilton Anxiety* (HAMA) and *Depression* (HAMD 21) *scales* between 11 a.m. and 1 p.m. by the same interviewer (DN) on the second day of their stay in our laboratory, after their first night of polysomnographic recording. Generally proposed cut-offs, for anxiety disorders and depression, are scores>20 on the HAMA and scores>13 on the BDI respectively.

2.3.4. Electrophysiology

Event-Related Potentials (ERPs) and VCN were recorded with a Medelec Sapphire 4 Premiere® device (Medelec Co.™, Surrey, UK). For P300 assessment we used a standard auditory oddball paradigm. The P300 is a positive ERP component peaking at approximately 300 ms after stimulus onset. The P300 is typically elicited by novel and low probability (rare) stimuli, but is also sensitive to other parameters such as task relevance. Auditory P300 reflects cognitive processing and decision making in particular (Hall, 1990). For ERPs recording, needle electrodes were placed at Fz, Cz and Pz (International 10–20 system). P300 ERP was always carried out before EEG recording (see below).

In a separate room from the ERPs, daytime EEG was also recorded on the third day of the patient's stay in the sleep lab between 9 a.m. and 10:30 a.m. after a second night of polysomnographic recording. EEG was assessed with a 21-electrode ANT Cognitrace EEG device (eemagine™, Berlin, Germany) and the eemagine© acquisition program (eemagine©, EEG version 3.2.0.2, Medical Imaging Solutions Inc. GmbH, Berlin, Germany). Low-pass and high-pass cut-off filter for fast Fourier transformation (FFT) were set at 0.53 and 40 Hz respectively. All EEG recordings comprised an intermittent stroboscopic light stimuli trial and a 3-minute hyperventilation essay. Time schedules and respective testing conditions were identical for all included subjects. All electrophysiological analyses were performed by a trained technician unaware of the aims of the study, among other clinical routine activities.

For FFT-derived spectral power analyses, we visually selected two 10-second artefact-free epochs for each subject. Power values for each electrode and for each subject were then averaged for these two selected epochs.

2.4. Statistics

All variables in each of the groups were compatible with the use of parametric tests.

Between-group comparisons involving continuous data were computed using MANOVA with single factor (subject group). Contrast tests between the groups were performed when ANOVAs showed significant outcomes. Explorative pairwise correlations were computed using Pearson's product moment 'r'. Hypotheses tests were two-sided and carried out at a 5% significance level. Trends were marked between brackets at a 10% level. All results were expressed as mean ± standard deviation. Analyses were computed using SPSS 16® (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Sample characteristics (Table 1)

Mean age among subject groups (all females) ranged from 36.73 (7.1) to 40.40 (4.3). Although SAHS patients were numerically older, the age difference was not found to be significant among subject groups. Despite not controlling for IQ, education levels were strictly balanced among groups and all subjects had at least a high school degree. SAHS patients showed the highest body mass indices (BMI) whereas BMI was similar between CFS patients and HCs. As expected CFS patients showed the highest fatigue levels and SAHS patients showed the highest sleepiness levels among groups. Although clinically not significant and within normal ranges, according to usual cut-offs, the remaining fatigue levels in the SAHS and subjective sleepiness levels in the CFS group respectively, were significantly higher than in HCs. Affective symptoms of both patient groups showed higher scores than in the HC group on all scales. While showing similar levels of depressive symptoms on the HAMD, the HAMA and the BDI group, respectively, showed significantly higher symptom intensities in CFS than in SAHS patients. Though being significantly worse than in HCs, perceived sleep quality (PSQI) did not differ between patient groups. (Table 1)

3.2. Comparisons of cognitive and behavioural measures (Table 2, Figs. 1, 2a and b)

Excepted for the AVLT recognition and the backward task on the digit span, all neuropsychological tests showed significantly lower performances in patients than in HC's.

Only the forward task on the digit span, the symbol span and the mean hit rates (right and left) of the FTT discriminate between patient groups showing lowest performance levels in SAHS patients (Table 2). Fig. 1 graphically illustrates the numerical scores of verbal memory performances in the AVLT, showing a similar pattern for each trial. Fig. 2a and b illustrates the mean hit rates of each FTT trial (1 to 5) for the right and left hand in each group. Comparisons of these measures were also performed with a MANCOVA using BMI as a covariate; however, the latter did not significantly affect the outcome results. We therefore consider within the present that BMI does not influence the observed differences in cognitive and behavioural measures among subject groups (results not shown). Although SAHS patients systematically showed the lowest hit rates among subject groups, only CFS patients did not show an improvement of their initial hit rate (trial 1) at their last assay (trial 5), in particular during the dominant hand trials. The trend lines of the latter in both SAHS and HC show positive slopes, whereas only CFS patients' trend lines appear to show a "fatigability effect" (negative slope) instead of an expected "learning effect" (increase of performance over the successive trials) as for the two other groups.

Table 1
Descriptive variables.

Variable	CFS ($N=15$)	SAHS ($N=15$)	CTRLS ($N=16$)	MANOVA		η^2	CFS/CTRLS Fisher LSD	SAHS/CTRLS Fisher LSD	CFS/SAHS Fisher LSD
				F	***P***		*P*	*P*	*P*
Age	36.73(7.1)	40.40(4.3)	36.94(6.1)	1.802	NS	.077			
BMI	23.33(4.1)	34.23(6.1)	20.86(1.9)	41.37	0.000	0.658	NS	0.000	0.000
HAMD	8.67(2.9)	7.73(2.5)	1.94(1.4)	37.37	0.000	0.635	0.000	0.000	NS
HAMA	15.20(3.4)	11.26(2.3)	3.5(2.1)	77.27	0.000	0.782	0.000	0.000	0.000
BDI-13	8.60(5.3)	5.80(2.5)	0.75(1.0)	20.82	0.000	0.492	0.000	0.031	0.000
PSQI	9.20(4.2)	9.33(4.1)	2.81(1.4)	17.90	0.000	0.454	0.000	0.000	NS
FSS	5.83(1.2)	3.11(0.7)	1.59(0.9)	79.19	0.000	0.786	0.000	0.000	0.000
ESS	6.34(3.3)	13.2(1.8)	3.75(2.2)	57.65	0.000	0.728	0.007	0.000	0.000

Legend: Chronic fatigue syndrome (CFS); sleep apnea–hypopnea syndrome (SAHS); Control subjects (CTRLS); Body Mass Index (BMI); Hamilton Depression Rating Scale 21-items (HAMD); Hamilton Anxiety Scale (HAMA); Beck Depression Inventory short form 13-items (BDI-13); Pittsburgh Sleep Quality Index (PSQI); Fatigue Severity Scale mean score (Total/9, FSS); Epworth Sleepiness Scale (ESS). Trends are marked between ( ). The given effect-sizes (η^2) are partial eta squares.

Table 2
Cognitive and behavioural measures.

Variable	CFS ($N=15$)	SAHS ($N=15$)	CTRLS ($N=16$)	MANOVA			CFS/CTRLS Fisher LSD	SAHS/CTRLS Fisher LSD	CFS/SAHS Fisher LSD
				F	***P***	η^2	*P*	*P*	*P*
A1	7.07(1.5)	6.00(1.3)	9.19(2.1)	14.53	0.000	0.403	0.001	0.000	(0.089)
A2	9.40(0.9)	8.67(1.9)	11.63(2.1)	12.38	0.000	0.365	0.001	0.000	NS
A3	10.67(1.3)	9.73(2.9)	12.88(1.5)	9.81	0.000	0.313	0.004	0.000	NS
A4	12.00(1.5)	11.27(2.3)	13.38(1.1)	6.25	0.004	0.225	0.029	0.001	NS
A5	12.47(1.3)	12.13(1.3)	14.00(0.8)	10.84	0.000	0.335	0.001	0.000	NS
B1	5.67(1.5)	4.73(1.2)	7.01(1.7)	8.83	0.001	0.291	0.018	0.000	(0.098)
A6	10.87(2.4)	9.8(2.0)	12.87(2.1)	8.83	0.001	0.291	0.014	0.000	NS
A7	11.27(1.8)	10.13(1.6)	13.19(2.0)	8.01	0.001	0.271	0.005	0.000	(0.092)
AVLT tot	57.40(16.5)	50.13(10.1)	61.06(6.2)	3.51	0.038	0.140	NS	0.012	(0.094)
RECOG	13.47(1.3)	13.07(3.3)	14.13(1.2)	0.95	NS				
DIGITfw	9.13(1.0)	7.2(1.4)	10.00(1.4)	11.68	0.000	0.352	NS	0.000	0.002
DIGITbw	6.40(1.6)	5.6(2.1)	6.87(1.7)	1.87	NS				
SYMBO	58.47(6.5)	46.07(10.4)	65.31(7.3)	21.61	0.000	0.501	0.026	0.000	0.000
FTRmean	51.77(4.0)	46.04(3.8)	55.41(4.7)	19.19	0.000	0.472	0.021	0.000	0.001
FTLmean	47.93(3.8)	42.31(6.7)	51.61(9.2)	6.92	0.002	0.243	NS	0.001	0.033
FTR1	51.13(4.8)	41.13(4.6)	51.56(7.3)	15.82	0.000	0.424	NS	0.000	0.000
FTR2	52.01(7.3)	46.80(4.1)	54.93(5.5)	7.68	0.001	0.263	NS	0.000	0.019
FTR3	54.73(4.4)	47.40(6.7)	56.00(5.9)	9.86	0.000	0.315	NS	0.000	0.001
FTR4	51.60(4.9)	46.87(5.3)	56.87(6.7)	11.84	0.000	0.355	0.014	0.000	0.029
FTR5	49.40(3.8)	48.00(4.1)	57.68(5.3)	21.22	0.000	0.497	0.000	0.000	NS
FTL1	48.27(4.8)	41.00(6.4)	52.19(9.2)	9.79	0.000	0.313	NS	0.000	0.008
FTL2	48.80(4.5)	42.13(7.8)	51.68(9.1)	6.60	0.003	0.235	NS	0.001	0.019
FTL3	48.93(4.4)	41.86(7.5)	50.50(9.7)	5.54	0.007	0.205	NS	0.003	0.015
FTL4	47.53(3.7)	42.67(6.5)	51.62(9.8)	5.92	0.005	0.216	NS	0.001	(0.073)
FTL5	46.13(3.4)	43.86(6.4)	52.06(9.3)	5.87	0.006	0.214	0.021	0.002	NS

Legend: Rey Auditory Verbal Learning Test total score and trials 1 to 5 (A1–A5, AVLT tot); AVLT immediate recall (A6); AVLT delayed recall (A7); AVLT interference list (B1); Digit span forward (fw), backward (bw) and total score (DIGIT tot); Symbol span score after 90 s (SYMBO); finger tapping test (FTT) overall mean right (dominant) hand hit rate (FTRmean); FTT overall mean left hand hit rate (FTLmean). FTT right hand trials mean hit rates (FTR1–5); FTT left hand trials mean hit rates (FTL1–5). Trends are marked between ( ). The given effect-sizes (η^2) are partial eta squares.

3.3. Pairwise correlation

Correlation analysis was used to investigate the relationships between fatigue and sleepiness (as measured by the FSS and the ESS respectively) and cognitive variables (AVLT, digit span, DSST, FTT). These explorative pairwise correlations mainly showed one significant result between sleepiness (ESS) and the total AVLT score in the SAHS group only ($r=0.718$, $p=0.003$). Fatigue was not associated to any cognitive measure in the CFS group. Fatigue and sleepiness also showed no significant correlations to each other in both patient groups.

3.4. Descriptive comparisons of electrophysiological variables

One CFS patient and two SAHS patients refused to undergo daytime EEG and evoked potentials. The EEG and the P300 ERP of two HC subjects could not be recorded because of unavailability of the technician at the moment of their stay in the hospital. For further technical reasons (local network crash) the data of another SAHS and of two HC subjects were lost or seriously damaged (partial data loss). A MANOVA was carried out to determine the spectral power values among electrodes between subject groups. Only significant outcomes or comparisons showing a trend were included in post-hoc analysis. Table 3 shows the MANOVA and post-hoc tests with 13 significant differences in theta power and two significant differences in beta power. CFS patients showed significantly higher theta power values, on 11 electrodes, than SAHS patients but only on two electrode-sites compared to controls (Table 3, Fig. 3). P300 latencies and amplitudes did not differ between groups (Table 3). None of the patient groups showed a significant relationship between ERPs (P300) and either sleepiness or fatigue.

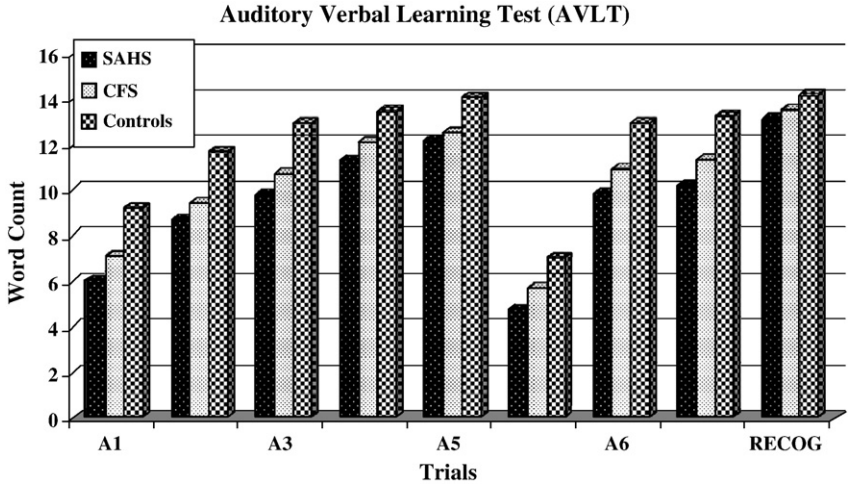

Fig. 1. Illustration of AVLT scores among subject groups. *Legend*: Auditory Verbal Learning Test (AVLT) trials 1 to 5 (A1–A5); AVLT interference list trial (B1); Recall trials (A6 immediate, A7 delayed); AVLT recognition trial (RECOG). AVLT total scores and comparative statistics between groups are given in Table 2.

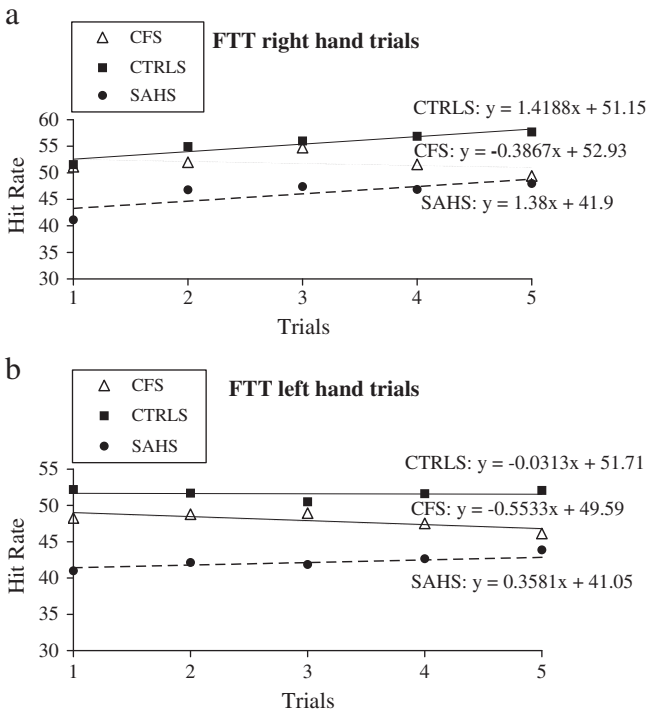

Fig. 2. a: Mean right hand hit rates among trials during the FTT. b: Mean left hand hit rates among trials during the FTT. *Legend*: Evolution of hit rates during the finger tapping test (FTT) for each trial (1 to 5) by subject groups. NB: Overall mean hit rates (right and left hand) are given in Table 2. Right hand derived trend lines show a negative slope ('fatigability') in CFS patients only.

4. Discussion

Despite the repeated mention of their crucial importance, clinical studies contributing to the differentiation of sleepiness and fatigue are still cruelly lacking in the general medical literature. One possible way to increase the knowledge about specific aspects of both conditions is to investigate patient groups that can serve as respective models for fatigue-or sleepiness associated conditions.

In the present study we attempted to compare cognitive and behavioural psychomotor performances in a standard test battery between patient groups presenting mainly with a sleepiness complaint (SAHS group) or a fatigue complaint (CFS group). In addition we described electrophysiological EEG and ERP (P300) derived data in a subgroup. Patient groups were furthermore compared to HCs of similar age. Both SAHS and CFS patients presented with similar cognitive complaints in previous reports. Therefore, our main hypothesis stated that we would not observe any significant differences in their respective impairment profile as assessed by neuropsychological routine testing.

4.1. Symptom scales, cognitive and psychomotor performances among subject groups

Scores were highest for CFS patients, but both patient groups showed higher affective symptom intensities than HCs. Though worse in patients compared to HCs, sleep quality perception did not differ between patient groups.

With the exception of the digit span and the AVLT total score which did not differ between CFS patients and HCs, all other neurocognitive measures showed lower performances in patients than in HCs. Hence both fatigue- and sleepiness-associated conditions that are presented here showed diminished cognitive functioning especially on the verbal memory recall trials. Indeed, only the mean left and right hit rates on the FTT and the performances on the forward task of the digit span and the DSST discriminated between patient groups showing SAHS patients with a higher impairment profile.

Albeit fatigue and sleepiness are very different clinical conditions by definition with very different possible pathophysiological pathways, the potential associated impact on cognitive function seems, to some extent, similar here. In contrast to sleepiness, however, the intensity (or severity) of fatigue was not correlated to cognitive dysfunction in the CFS group in the present study. One could speculate that motivational aspects might have a higher impact in fatigue-related conditions than in sleepiness-associated disorders.

Despite lower overall hit rates we found CFS patients with a different pattern of performance progress on the FTT. While both SAHS patients and control subjects tended to increase their performances over the different trials, only CFS patients showed systematically a 'fatigability' profile on the FTT with lower hit rates on the last trial than on the first trials. This observed effect was particularly striking in testing the FTT of the dominant hand.

One can speculate that the FTT is a behavioural psychomotor measuring instrument that permits one to assess performance related

Table 3
Electrophysiological data.

EEG Site (μV^2)	CFS ($N=14$)	SAHS ($N=12$)	CTRLS ($N=12$)	MANOVA		η^2	CFS/CTRLS Fisher LSD	SAHS/CTRLS Fisher LSD	CFS/SAHS Fisher LSD
				F	***P***		*P*	*P*	*P*
Fp1 θ	3.15(1.7)	0.63(0.4)	1.40(0.9)	6.698	0.005	0.368	0.025	NS	0.002
F3 θ	0.93(0.5)	0.42(0.2)	0.74(0.4)	3.216	(0.058)	0.219	NS	(0.08)	0.02
C3 θ	0.57(0.2)	0.27(0.1)	0.61(0.4)	2.911	(0.075)	0.202	NS	0.05	(0.038)
T3 β	0.54(0.5)	0.39(0.2)	0.75(0.6)	3.562	0.045	0.237	0.023	0.039	NS
T3 θ	1.03(0.4)	0.42(0.1)	1.00(0.5)	5.552	0.011	0.326	NS	0.011	0.005
P3 θ	0.82(0.4)	0.35(0.2)	0.70(0.5)	3.595	0.044	0.238	NS	0.013	NS
Cz θ	0.86(0.6)	0.28(0.2)	0.89(0.5)	4.201	0.028	0.268	NS	0.025	0.012
Pz θ	0.79(0.3)	0.3(0.1)	1.03(0.8)	3.226	(0.058)	0.219	NS	0.025	0.05
Fp2 θ	2.40(1.5)	0.75(0.4)	1.80(1.5)	2.831	(0.080)	0.198	NS	NS	0.026
F4 θ	0.89(0.4)	0.29(0.07)	0.55(0.3)	6.888	0.005	0.375	0.049	NS	0.001
F8 θ	2.21(1.5)	0.74(0.3)	1.89(1.8)	2.836	(0.079)	0.198	NS	NS	0.027
C4 θ	0.63(0.3)	0.21(0.09)	0.60(0.3)	5.884	0.009	0.338	NS	0.037	0.002
T4 θ	1.23(0.4)	0.64(0.3)	1.07(0.7)	3.321	(0.054)	0.224	NS	NS	0.017
T6 θ	1.43(0.7)	0.53(0.3)	1.36(1.2)	3.350	(0.053)	0.226	NS	(0.067)	0.019
O2 β	1.19(1.4)	0.83(0.5)	1.33(0.5)	3.654	0.042	0.241	0.024	0.032	NS
P300(L)	283.15(31.1)	302.0(27.6)	287.1(27.5)	0.768	NS	0.049			
P300(A)	17.5(6.8)	15.2(5.9)	20.7(6.1)	1.736	NS	0.193			

Legend: Table 3 shows significant outcomes or trends of MANOVA for spectral power bands (absolute power values) per electrode-site between subject groups on the daytime EEG and P300 related parameters. Spectral power values (μV2) were computed by averaging two artefact-free, visually chosen, 10-second epochs. P300 latencies (L) are expressed in milliseconds and amplitudes (A) in μV. The given effect-sizes (η^2) are partial eta squares.

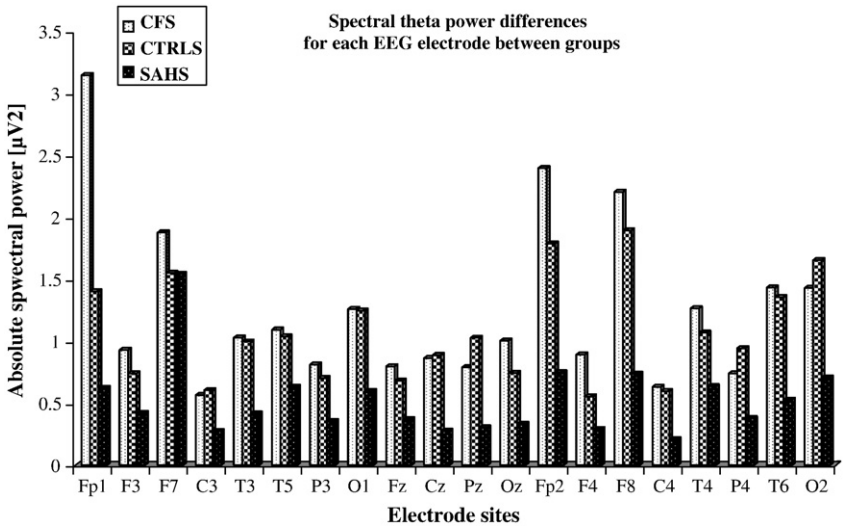

Fig. 3. Comparative illustration between EEG spectral theta power bands. *Legend*: Fp1 to O2: EEG derivations according to the 10/20 standard EEG-system; Frontal (F); Temporal (T); Parietal (P); Occipital (O). Although not always statistically significant, CFS patients displayed higher theta power values than the two other groups in most cases (15 out of 20 EEG derivations, see also Table 3). Only absolute beta power of the O2 and T3 sites showed additional significant differences between groups (see Table 3).

to altered vigilance and motor speed (sleepiness) and to the kinetics of an exhaustion state (fatigability). It had been stated before that vigilance implies both the degree of arousal on the sleep–wake axis and the level of cognitive performance (Oken et al., 2006). To this extent, the latter is corresponding to the definitions of sleepiness (altered vigilance, drowsiness, and attention impairment) and fatigue (more rapid exhaustion after a given mental or physical effort and lowered global energy sensation). Perhaps we should therefore think of similar strategies in the future to further increase the possible objective discriminations of sleepiness and fatigue.

4.2. Electrophysiology

Descriptive electrophysiological data showed previously mentioned numerically higher EEG theta power in CFS patients. Nevertheless, despite acceptable effect-sizes, descriptive electrode-site comparisons between groups only showed a few significant results between patient groups and even less compared to HCs. Interestingly, P300 ERPs did not show significant differences between groups. As mentioned before, it seems as if ERPs such as the P300 are perhaps not sensitive enough to discriminate between groups with moderate levels of global cognitive impairment profiles.

4.3. Limitations

(1) Whether the testing used in this study is the most appropriate for SAHS or CFS is unclear. Nevertheless several authors have used the AVLT and the FTT in previous studies on SAHS and CFS patients. (2) Objective sleepiness measures were not performed in the present study. However, as we previously reported in CFS patients a potential overlapping in subjective sleepiness complaints only (ESS only and not on the MSLT), we attempted to avoid this in selecting only pure CFS patients with an ESS score below 10. (3) Only female subjects were studied here mainly because of the high female/male sex ratio in the natural prevalence of CFS. (4) Subject groups have not been matched for their global IQ. Nevertheless all included subjects had at least a high school degree and further study degrees and education levels were balanced between groups.

5. Conclusions

In conclusion we showed for the first time that in a direct comparison, fatigue- and sleepiness-associated conditions can both present with potentially similar cognitive impairment profiles, when compared to a healthy control group. Although the present results also suggest that altered vigilance in sleepiness-associated conditions can show even lower psychomotor performances on the FTT and higher attention deficits in standard tests such as the digit or the DSST. Furthermore, fatigue only presents here with a systematic lack of performance increase on the FTT.

We think that this kind of research, where the investigated symptoms and signs are potentially related to both conditions (fatigue and sleepiness), is one fertile path leading to a further increase of knowledge about the pathophysiology of, often difficult to treat, chronic fatigue and to contribute to the necessary distinction from, often easy-to-treat, daytime sleepiness.

Further research should therefore also investigate other models of fatigue (e.g., multiple sclerosis, auto-immune diseases, insomnia, major depression, cancer) and sleepiness models (e.g., narcolepsy, partial sleep deprivation).

The present findings should also be expanded to other population samples (e.g., male subjects) and should be extrapolated to subjective and/or objective fatigue and sleepiness conditions disregarding clinical diagnostic categories. Another interesting and promising approach would be to extend cognitive and psychomotor tasks in both models to functional neuroimaging and topographical EEG assessments.

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