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Independency of Selective Neuropsychological Dysfunctions from Subjective Daytime Sleepiness in Drug-Naive Patients with Narcolepsy

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Abstract

Besides key symptoms of narcolepsy such as excessive daytime sleepiness, cataplexy, and disturbed nighttime sleep, patients affected by the disease also suffer from cognitive deficits, particularly impairments in attention, concentration, and various memory skills. However, it is still not fully understood to what extent cognitive impairments are independent of daytime sleepiness. In this study we aimed at identifying the taxonomy of neuropsychological dysfunctions in patients with narcolepsy without any stimulant or specific narcolepsy medication and the degree of independency of specific cognitive impairments of subjective daytime sleepiness. We expected that memory impairments, prefrontal dysfunctions, and disturbed emotion processing are independent of subjective daytime sleepiness and age. 22 patients with narcolepsy and 89 healthy controls were assessed by a comprehensive neuropsychological testing battery, psychological questionnaires on depression, alexithymia, as well a questionnaire on general daytime sleepiness. We found that narcolepsy patients exhibited independent of daytime sleepiness and age, significant deficits in tonic attention, set-shifting and in the conscious experience of arousal associated with emotions. Our results show for the first time that narcolepsy itself may lead to neuropsychological deficits that cannot be explained by subjective daytime sleepiness or aging-related cognitive decline. We propose that these novel insights are of considerable scientific and clinical relevance.

Keywords: Narcolepsy • Neuropsychological dysfunctions • Daytime sleepiness • Attention • Executive functions

Introduction

Narcolepsy is a chronic neurological disorder, which is primarily related to a deficiency of orexin. Orexin is a neuropeptide that is dominantly produced in the subthalamus and plays a major role in the regulation of sleep-wake behavior and vigilance. In addition to these functions, orexin also appears to influence thermoregulation and eating behavior. Approximately one in 2.500 people is affected by the disease [1-4]. Main symptoms of the disease are excessive daytime sleepiness (EDS), cataplexy, disturbed nighttime sleep, sleep-related hallucinations, and sleep paralysis [5]. Moreover, patients frequently suffer from cognitive deficits, in particular, impairments in attention, concentration, executive functioning and various memory skills (for a review see [6]). It has been proposed that all or at least some of these neuropsychological disturbances may depend on EDS [7]. However, the relationship between narcolepsy and neuropsychological deficits is still not yet fully understood. It remains to be clarified, which specific cognitive domains are affected by the disease and to what extent selective cognitive dysfunctions are independent of EDS.

To date, research has particularly focused on impaired attention in patients with narcolepsy. Slower reaction times and a decrease in performance over time have been demonstrated for the domain of alertness [7-10]. Some studies also showed impairments of sustained attention and vigilance in terms of increased error rates and error variability [9,11-14]. For divided attention, slower performance and variable reaction times were reported under conditions of high task complexity [8-10,15]. Some studies did not find impairments in simple alertness tasks, but decreased reaction times in more complex tasks such as the executive control of attention [7,16]. These findings suggest that dysfunctions of executive control of attention may play a key role in impaired attentional performance of patients with narcolepsy.

There is evidence for disturbances of subdomains of executive functions in patients with narcolepsy. They may show slowed response inhibition, with intact correctness of responses [7,17], impaired cognitive flexibility [7] and enhanced time for the completion of set-shifting tasks [17]. The review of Filardi et al. does not indicate impairments for the domains of logical reasoning and spatial planning. Subjectively, patients with narcolepsy often report memory problems [6,15]. Empirically, however, these could not be convincingly proven. Recent studies showed mild deficits of various memory skills in patients with narcolepsy [15,18], but these could also be a result of daytime sleepiness. Basically, narcolepsy type 1 patients seems to show mild deficits in memory consolidation [19,20] and working memory [7,21]. Patients with narcolepsy type two showed an increased error rate in the study of Bayard et al. but no performance impairment in reaction time for working memory [7].

Patients with narcolepsy (type 1) appear to have several deficits in emotion processing. Patients show less cardiovascular, electro dermal and autonomic as well as muscular reactivity and decreased amplitudes of the N2 and P3 components for unpleasant stimuli [22]. Furthermore, patients' responses to emotional stimuli appear to be less arousing and pleasant, and patients show less of their emotions [23]. The quality of life of narcolepsy patients is severely impaired. This enormous symptom burden extends to physical and psychological impairments [24]. In particular, social and emotional dysfunctions may act as severe stressors for patients with narcolepsy.

In this study we aimed at identifying the taxonomy of neuropsychological

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dysfunctions in patients with narcolepsy and the degree of independency of specific cognitive impairments of self-reported daytime sleepiness. We expected that dysfunctions in emotion processing, long-term memory, and prefrontal functions such as executive performance, attention, and working memory are mostly independent of self-reported daytime sleepiness.

Methods

Sample

22 patients and 89 healthy control subjects were enrolled from the out-patient center for narcolepsy and hypersomnias and at Witten/Herdecke University between 2019 and 2022. Inclusion criteria for the patients included male or female gender with diagnosed narcolepsy Type 1 or Type 2 (according to ICSD-3) and no stimulant or specific narcolepsy medication taken at the time of the study. Other medication without major impact on the central nervous system were allowed (i.e., medication against blood pressure). Further inclusion criteria for the entire sample were age >18 years, fluent written and spoken German language, and unimpaired or corrected vision and hearing. Exclusion criteria were IQ<90, serious medical illnesses (e.g., oncological diseases, chronic infections), and serious psychiatric illnesses (e.g., psychoses, personality disorders). Study participants were assessed using standard neuropsychological testing instruments and psychological questionnaires. The study participants were informed about the aims, procedures, and test procedures of the study and gave their written informed consent. The study complied with the current version of the Declaration of Helsinki and was approved by the ethics committee of Witten/Herdecke University.

Study design

Patients and control subjects underwent a comprehensive and differential neuropsychological and psychological assessment to identify neurocognitive performance, emotion processing, and subjective daytime sleepiness in patients with narcolepsy and healthy individuals.

Neuropsychological testing battery

Neuropsychological diagnostics focused on attention, executive functions, working and long-term memory, and social cognition. The following standard testing instruments available in the German language area were used: Digitspan, Blockspan, Trail Making Test (TMT-A and TMT-B), d2-R Test, Rey-Osterrieth-Complex-Figure Test, Multiple Choice Vocabulary Test (MWT-B), Test Battery for Attention, Sustained Attention to Response Task, Coding Subtest of WAIS-V (DSST), Reading-Mind-in-the-Eyes Test [25-33].

Medical and psychological questionnaires

For the assessment of narcolepsy symptoms, subjective daytime sleepiness, depression, alexithymia, and empathy, the following well established questionnaires established in the German language area were used: Social formulas for estimating the intelligence quotient according to Wechsler (IQ), Beck Depression Inventory Revised, Toronto-Alexithymia-Scale-26 (TAS-26), Bermond-Vorst Alexithymia Questionnaire, Epworth Sleepiness Scale (EDS), The Edinburgh Inventory [34-39].

Statistical analysis

After checking the prerequisites (see Results section), parametric test procedures were used for the statistical analyses. The significance level was set at p<.05, adjusted for alpha-error-accumulation. Individual missing data points were substituted with Measures of Location Scales. To assess presumed performance differences in neuropsychological performance parameters between healthy subjects and narcolepsy patients, controlled for sleepiness and age, a one-factor MANCOVA followed by one-factor ANOVA's (post-hoc tests) was calculated. For all statistical analyses SPSS 27 (IBM Corp. Armonk, NY) was used. Because of the small group size, it was not possible to separate narcolepsy type 1 from narcolepsy type 2. Therefore, following the main analyses, independent Mann-Whitney-U-Tests were performed for these two separate groups. This analysis was performed for the significant values as well as for some descriptive values between narcolepsy type 1 and type 2. This was carried out in order to be able to make more differentiated statements on whether differences between healthy persons and narcolepsy patients might be due to differences between type 1 and type 2 narcolepsy (Table S1).

Results

The control group was on average ~8 years older than the experimental group. Women were overrepresented in the control group compared to the patient group (77.9% vs. 40.9%). No significant difference in IQ and self-reported daytime sleepiness at momentary assessment was found between patient group and control group (p<0.05). Table 1 summarizes the demographic characteristics of the sample, divided by group classification. 21 outliers were excluded from statistical analyses. Most, but not all variables were normally distributed. A single-factor MANCOVA, which is a robust statistical model for this condition, was used for parametric statistical calculations. Some of the initial single variables measuring aspects of the same construct were excluded due to multicollinearity. Median values of alertness measures with and without warning signal also indicated multicollinearity and were therefore merged into one variable. No multivariate outliers were found, as measured by Mahalanobis distance. Linearity of dependent variable pairs was confirmed for the two levels of the MANCOVA's single factor. Homogeneity of variance and the covariance matrices was given for most, but not all variables. Accordingly, Pillai trace, Wilks-Lambda, Hotelling trace, and Roy's Largest Characteristic Root statistics were used to evaluate authenticity of significance. Homogeneity of the regression slopes was given for all covariates (p>.05).

Table 1. Descriptive statistics of the narcolepsy and control group.

		Control group (n=68)						Narcolepsy group (n=22)					
		Frequency	Relative frequency	M	SD	Min.	Max.	Rrequency	Relative frequency	M	SD	Min.	Max.
Age		-	-	23.69	4.28	18	47	-	-	31.91	14.78	18	75
IQ		-	-	123.54	10.7	93.16	139.68	-	-	124.67	13.54	95	140
Sex	Female	53	77.9	-	-	-	-	9	40.9	-	-	-	-
	Male	15	22.1	-	-	-	-	13	59.1	-	-	-	-
School graduation	Baccalaureate	63	92,6	-	-	-	-	13	59,1	-	-	-	-
	Secondary school diploma	0	0	-	-	-	-	4	18.2	-	-	-	-
	Lower secondary school graduate	0	0	-	-	-	-	4	18.2	-	-	-	-
	None	0	0	-	-	-	-	1	4,5	-	-	-	-

Handedness	Left-handed	23	33.8	-	-	-	-	8	36.4	-	-	-	-
	Ambidextrous	3	4.4	-	-	-	-	1	4.5	-	-	-	-
	Right-handed	35	51.5	-	-	-	-	9	40.9	-	-	-	-
Note: The following variables showed missing values: Control group: variable high school graduation n=63, control group: variable handedness n=61; narcolepsy group: variable handedness n=18													

Results of the single-factor MANCOVA demonstrated a statistically significant difference between patients with narcolepsy and controls for the combined dependent variables, controlled for age and raw EDS score, $F(35,50)=1.685$, $p<.05$, partial $\eta^2=.541$, Wilk's $\Lambda=.459$. A posthoc single factorial ANOVA was performed for each dependent variable. There was a statistically significant difference between narcolepsy patients and controls for the standard deviation of the SART test ($F(1, 84)=14.19$, $p=.001$, partial $\eta^2=.15$), alertness without warning signal: omissions ($F(1, 84)=4.202$, $p=.043$, partial $\eta^2=.048$), the TMT-B ($F(1, 84)=4.453$, $p=.038$, partial $\eta^2=.050$), the sum score of the cognitive factor subscale of the BVAQ ($F(1, 84)=6.022$, $p=.016$, partial $\eta^2=.067$), and the total sum score of the BVAQ ($F(1, 84)=4.945$, $p=.029$, partial $\eta^2=.056$). Figure 1 visualizes the estimated marginal means of the significant variables. Table 2 summarizes between-group post-hoc tests of the single-factor MANCOVA and corresponding descriptive values for all variables. Results show higher SART standard deviations, a higher number of omissions in alertness without warning signal, longer TMT-B completion times, higher BVAQ scores on the cognitive factor subscale and the total sum score of the BVAQ for the patient group compared to controls.

Table 2. Tests of between-subjects effects for the narcolepsy- and control group, including descriptive statistics.

Factor	Dependent variable	df	F	sig.	Partial η^2	M_1	SD_1	M_2	SD_2
Group allocation	SART AVG	1.00	0.01	0.92	0	363.81	40.05	369.01	63.61
	SART SD	1.00	14.19	0.00*	0.14	68	17.88	94.96	56.16
	SART PE	1.00	0.36	0.55	0	9.4	5.3	12.43	6.15
	SART ME	1.00	0.18	0.67	0	10.94	41.32	3.86	5.88
	TAP alertness without warning signal omissions	1.00	4.2	0.04*	0.05	0.07	0.26	0.33	1.08
	TAP alertness with warning signal omissions	1.00	0	0.98	0	0.01	0.12	0	0
	TAP alertness with and without warning tone median	1.00	3.17	0.08	0.04	231.82	28.6	266.76	73.73
	TAP divided attention errors	1.00	0	0.95	0	0.68	0.89	1.33	1.52
	TAP vigilance errors	1.00	0.02	0.89	0	4.66	6.03	7.82	8.46
	TAP vigilance median	1.00	0.85	0.36	0.01	606.78	96.82	681.36	132.53
	DSST	1.00	3.1	0.08	0.04	80.1	12.19	67.5	18.19
	RCFT copy	1.00	2.27	0.14	0.03	34.01	2.31	32.91	4.3
	RCFT memory quotient	1.00	0.76	0.38	0.01	146.46	31.5	124.77	37.75
	D2 error percentage	1.00	1.74	0.19	0.02	14.81	12.67	20.9	16.19
	D2 processed target objects	1.00	2.95	0.09	0.03	174.83	35.36	152.68	39.28
	D2 concentration	1.00	3.12	0.08	0.04	150.04	41.68	123.41	44.22
	TMT-A	1.00	1.62	0.21	0.02	23.77	8.15	24.68	10.3
	TMT-B	1.00	4.45	0.04*	0.05	51.14	16.83	72.59	36.32
	Digitspan forward	1.00	1.34	0.25	0.02	10.54	1.96	9.86	1.93
	Digitspan backward	1.00	0.03	0.87	0	9.94	2.3	8.14	2.05
	Blockspan forward	1.00	1.85	0.18	0.02	12.07	2.53	10.23	2.67
	RMET correct hits	1.00	0.64	0.42	0.01	27.02	2.6	23.09	4.23
	RMET correct positive hits	1.00	1.45	0.23	0.02	5.69	1.25	5	1.57
	RMET correct negative hits	1.00	0.54	0.46	0.01	9.55	1.37	8.18	1.97
	RMET correct neutral hits	1.00	0.03	0.85	0	11.78	1.7	9.91	1.85
	BDI	1.00	0.31	0.58	0	5.91	4.55	14.63	6.59
	MWT-B	1.00	4.27	0.05	0.05	29.15	2.72	24.9	5.72
	TAS-26 identifying feelings	1.00	2.82	0.1	0.03	13.5	4.03	17.09	5.02
	TAS-26 describing feelings	1.00	1.76	0.19	0.02	10.78	3.59	14.28	3.65
	TAS-26 externally oriented thinking style	1.00	0.18	0.68	0	12.98	2.99	14.2	3.14
	TAS-26 total score	1.00	2	0.16	0.02	37.26	7.11	45.57	8.73
	BVAQ AF emotionalyzing	1.00	0.43	0.51	0.01	26.84	2.91	25.26	2.2
	BVAQ AF fantasizing	1.00	0.27	0.61	0	26.14	2.52	25.32	2.66
	BVAQ AF sum score	1.00	0.02	0.9	0	52.97	3.96	50.58	2.85
	BVAQ CF identifying emotions	1.00	1.66	0.2	0.02	24.55	2.58	21.89	2.69
	BVAQ CF verbalizing emotions	1.00	0.01	0.91	0	24.2	2.1	24.05	2.87
	BVAQ CF analyzing emotions	1.00	0.55	0.46	0.01	24.8	2.63	22.63	3.92
	BVAQ CF sum score	1.00	6.02	0.02*	0.07	49.4	4.46	52.47	11.79
	BVAQ sum score	1.00	4.95	0.03*	0.06	102.38	5.95	103.05	12.34

Note: Control group n=68, Experimental group n=22; M_1=Mean of control group, SD_1=Standard deviation of control group; M_2=Mean of experimental group, SD_1=Standard deviation of experimental group; SART AVG=Sustained Attention to Response Task: average reaction time; SART SD=Sustained Attention to Response Task: reaction time standard deviation; SART PE=Sustained Attention to Response Task: pressed error; SART ME=Sustained Attention to Response Task: missed error; TAP Alertness / without warning signal – omissions=Test Battery for Attention: Alertness / without warning signal-omissions; TAP Alertness / with warning signal – omissions=Test Battery for Attention: Alertness / with warning signal – omissions; TAP Altertness with and without warning tone Median=Test Battery for Attention: Median of combined reaction time for Altertness with and without warning tone; TAP Divided attention Errors=Test Battery for Attention: pressed errors; TAP Vigilance errors=Test Battery for Attention: Vigilance pressed errors; TAP Vigilance Median=Test Battery for Attention: Vigilance median reaction time; DSST=Coding Subtest of WAIS-V; RCFT Copy=Rey-Osterrieth-Complex-Figure Test: Time to copy; RCFT Memory quotient=Rey-Osterrieth-Complex-Figure Test: Memory quotient; D2 test=D2-R-Test; TMT-A=Trail Making Test A; TMT-B=Trail Making Test B; RMET Correct hits=Reading-Mind-in-the-Eyes Test: Correctly recognized facial expressions; RMET Correct positive hits=Reading-Mind-in-the-Eyes Test: Correctly recognized positive facial expressions; RMET Correct negative hits=Reading-Mind-in-the-Eyes Test: Correctly recognized negative facial expressions; RMET Correct neutral hits=Reading-Mind-in-the-Eyes Test: Correctly recognized neutral facial expressions; BDI=Beck Depression Inventory Revised; MWT-B=Multiple Choice Vocabulary Test; TAS-26=Toronto-Alexithymia-Scale-26; BVAQ=Bermond-Vorst Alexithymia Questionnaire; BVAQ AF=Bermond-Vorst Alexithymia Questionnaire: Affective Factor; BVAQ CF=Bermond-Vorst Alexithymia Questionnaire: Cognitive Factor * p <.05

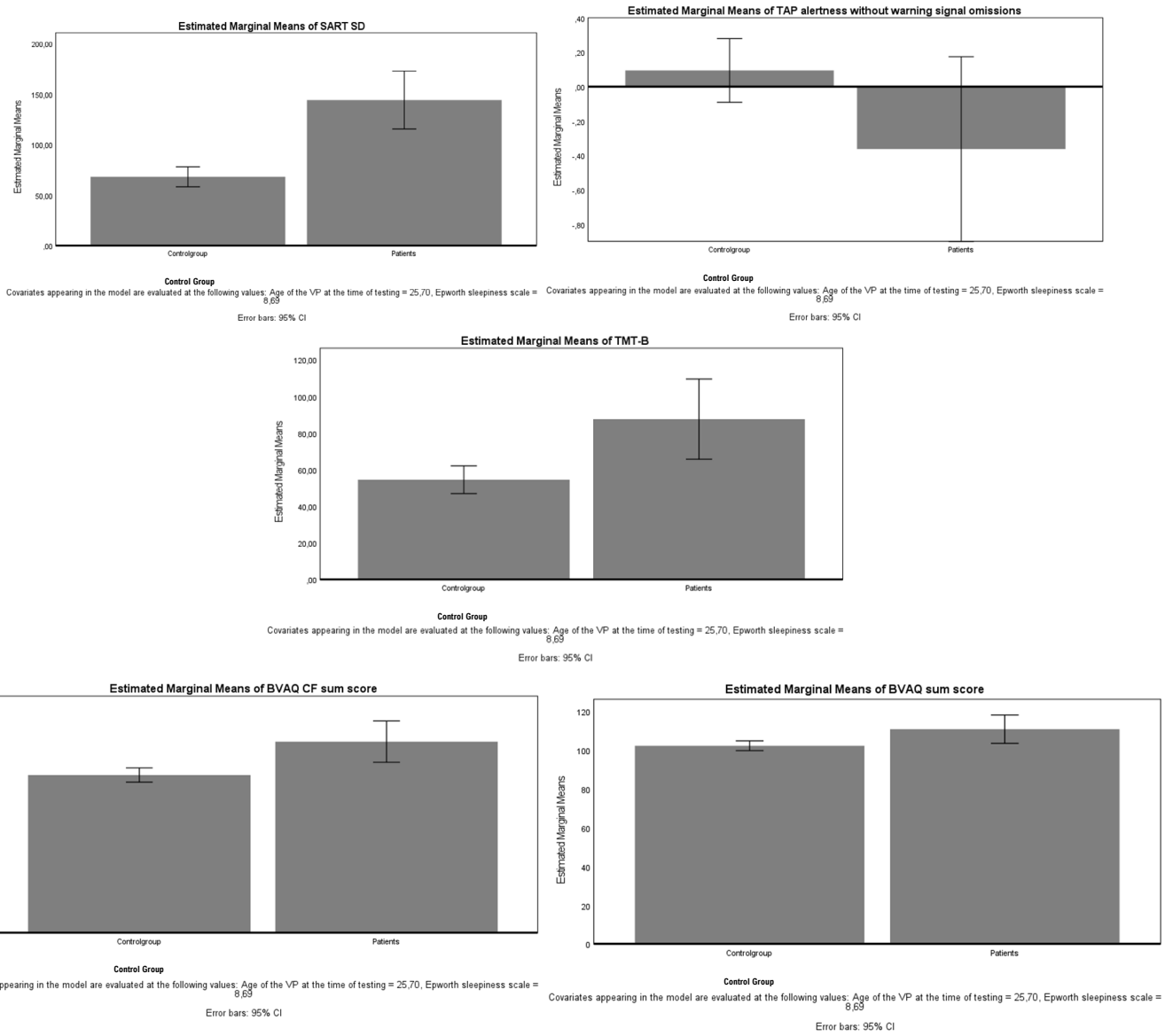

Figure 1. MANCOVA results for SART SD (A), TAP alertness without warning signal omissions (B), TMT-B (C), BVAQ CF sum score (D) and BVAQ sum score comparing healthy control subjects and patients with narcolepsy (without medication) controlled for age and subjective daytime sleepiness; SART SD=Sustained Attention to Response Task: reaction time standard deviation; TAP alertness without warning signal omissions=Test Battery for Attention: Alertness without warning signal-omissions; TMT-B=Trail Making Test B; BVAQ CF sum score=Bermond-Vorst Alexithymia Questionnaire: cognitive factor sum score; BVAQ sum score=Bermond-Vorst Alexithymia Questionnaire: sum score Alexithymia.

Discussion

In this study, we investigated neuropsychological dysfunctions, independent of self-reported daytime sleepiness and aging effects in patients with narcolepsy. Patients showed significant deficits in tonic attention and in set-shifting ability. Moreover, our data show specific symptoms of alexithymia in patients with narcolepsy. Our results show for the first time that narcolepsy itself may lead to neuropsychological deficits that cannot be explained by subjective daytime sleepiness or aging-related cognitive decline. We propose that these novel insights are of considerable scientific and clinical relevance.

Attention

The results demonstrate a selective impairment in tonic attention in patients with narcolepsy. This is specified by increased susceptibility to omission errors in tonic alertness. In contrast, alertness tasks including clue stimuli were unimpaired in the patients. Research on alertness in narcolepsy patients provides a heterogeneous picture. Although some studies demonstrated slower reaction times and a decrease in performance over time in alertness tasks [7-10], other studies do not corroborate these findings [7,15]. It should be noted that these studies did not control for daytime sleepiness, such that sleepiness may have confounded the data. These previous studies are thus not directly comparable with our approach. Increased omission errors occurring independently of daytime sleepiness, as demonstrated in our study, are supposed to be associated with a high response latency (>2 seconds) in the TAP subtest of tonic attention. The lack of a cue stimulus to direct attention may be the main explanation of our results. The concept of tonic attention refers to physiological activation and responsiveness of the organism. This dimension of physiological responsiveness is predominantly based on mesencephalic and right hemispheric cortical areas [40,41]. However, this aspect does not contribute to a neuroscientific understanding of our findings. Rather, results of our study suggest that other neurobiological factors need to be considered. Here, the well-known orexin deficiency, due to loss or partial loss of orexin neurons in the hypothalamus associated with narcolepsy comes into play [1,4,42,43]. Approximately 10% of individuals with narcolepsy type 2 and approximately 90% of individuals with narcolepsy type 1 show decreased orexin levels [1]. Orexin release is related to attentional processes in the medial prefrontal cortex, the cholinergic system in the basal forebrain, the dopamine system in the ventral forebrain, and noradrenergic neurons in the LC [44,45]. Especially norepinephrine is known to be involved in the regulation of phasic and tonic attention [46,47]. Impaired performance in tonic alertness could thus be due to diminished activity in mesencephalic and right hemispheric cortical areas caused by reduced activation of the locus coeruleus-norepinephrine system (LCNS). This dysregulation can be explained by a decline of orexin neurons in the hypothalamus and a concomitant reduced activation of the LCNS. This interpretation, however, is not in line with the finding of unimpaired phasic alertness in patients with narcolepsy in our study, since phasic alertness is to some extent also controlled by the LCNS. We propose that one reason for the absence of impairment could be the auditory stimulus preceding the target stimulus in the phasic alertness task. Processing of the cue stimulus via the auditory system may have initiated top-down processes by using alternative pathways, including nuclei of the Ascending Arousal System (ARAS). ARAS involvement may well explain activation of the LCNS and thus normal function of phasic alertness. This explanatory approach presumes, that functionality of the LCNS itself is unimpaired. Rather, dysfunction of a specific system providing input to the LCNS needs to be taken into consideration.

Interestingly, there is a study by McGregor et al. that reports an increased number of orexin neurons arising from chronic consumption of opiates resulted in enhanced orexin innervation and activity of the tyrosine hydroxylase in the LC [48]. Given that destruction of orexin neurons has opposite effects in the brain, both reduced orexin innervation and reduced tyrosine hydroxylase in the LC could occur in patients with narcolepsy. It would be useful to examine these two areas in more detail to determine the causes of declined tonic attention dysfunction in these patients. Similarly, it would be useful to include effects of opiate metabolism on LC in the development of novel medication for patients with narcolepsy. Opiate effects could perhaps slow down or partly reverse symptoms of narcolepsy [49,50]. Our results also showed, independent of subjective daytime sleepiness, a higher inter-variability of reaction times in sustained attention, with non-impaired in vigilance, divided attention, and attention under stress conditions. Our results are in contrast with previous studies that demonstrated impairment in some of these attentional domains for in patients with narcolepsy but did not control for daytime sleepiness [8-11,13-15,51]. The concerned attentional functions are not only related to activation of the LCNS. They also rely on the ARAS, which consists of a signaling pathway via cholinergic cell groups in the pons, pedunculopontine and laterodorsal tegmental nuclei, and another signaling pathway via monoaminergic cell groups such as the tuberomammillary nucleus (TMN), cell group A10, dorsal and median raphe nuclei, and the locus coeruleus (LC). In the wakefulness state, the LC, TMN, and serotoninergic raphe nuclei inhibit the ventrolateral preoptic nucleus (VLPO). Simultaneously, orexin neurons are disinhibited during wakefulness, exerting a reinforcing influence on the monoaminergic neurons. Conversely, activation of the VLPO promotes sleep and inhibits the nuclei of the ARAS [52].

Given that there is reduced baseline activation of the LC due to reduced orexin release in narcolepsy patients, two interpretations of the specificity of attentional decline in patients with narcolepsy emerge. Firstly, reduced baseline activation of the LC due to the lack of orexin leads to reduced inhibition of the VLPO and thus to increased sleepiness. This results in reduced activation of the nuclei of the ARAS because of the inhibitory effect of the VLPO on the ARAS. Then, reduced function of attentional functions apart from tonic alertness can be detected when sleepiness is not controlled. Secondly, the exclusion of subjective daytime sleepiness from the analyses indicates that impaired attentional functions are not related to reduce functionality of the subsystems of the ARAS, apart from the LC. Rather, they could be due to reduced activation of the ARAS by dysregulation of the VLPO induced by reduced inhibition by the LC, which is boosted by orexin neurons in healthy humans.

Executive functions, working memory, and visuospatial skills

Our results do not indicate impairments of verbal and visual working memory (measured by digit span and block span), executive processes of spatial working memory, and visuospatial short-term and working memory (measured by block span), processing speed, and visual attention (measured by the TMT-A), independent of subjective daytime sleepiness. Our data thus indicate that the previously reported dysfunctions in these domains may primarily be due to concurrent daytime sleepiness. However, impaired performance in the TMT-B, which primarily measures cognitive flexibility, working memory, and set-shifting abilities, could be detected in our study independently of subjective daytime sleepiness. These diverging results may be interpreted by two distinct explanatory approaches.

Firstly, one can assume that the TMT-B testing procedure produces a higher cognitive load compared to the other testing procedure, in which patients with narcolepsy did not show impaired performance. This would imply that the isolated targeting of the specific cognitive domains in tasks with low complexity will not be capable to identify neuropsychological impairments in narcolepsy patients. Rather, only simultaneous complex demands associated with multiple neuropsychological domains (e.g. working memory, processing speed, visuospatial function, and the executive functions, esp. set-shifting) will be able to detect neuropsychological impairments in patients with narcolepsy, independent of subjective daytime sleepiness. This could be due either to a dysfunctional allocation or a lack of neuropsychological resources when confronted with complex simultaneous cognitive demands. The second explanatory approach arises from our finding, that patients with

narcolepsy are unimpaired in single cognitive domains such as processing speed and visual-spatial search (TMT-A) and working memory (Digit Span), which are also relevant for TMT-B performance. Accordingly, the neuropsychological dysfunction that occurs independently of subjective daytime sleepiness in patients with narcolepsy must be related to a selective cognitive challenge of the TMT-B going beyond TMT-A and Digit Span demands. It is most likely, that the set-shifting component of the TMT-B is the key factor for cognitive dysfunction in patients with narcolepsy observed in our study. This argument is only partially consistent with previous studies. Moraes, Rossini and Reimao demonstrated impaired set-shifting in patients with narcolepsy, while studies of other authors did not corroborate these findings [17,21,53,54]. Note, daytime sleepiness was not ruled out as an influencing factor in all these studies. Recent animal studies in mice suggest that orexin deficiency may be crucial for deficient cognitive flexibility in patients with narcolepsy. Bayard, Croisier, Langenier and Dauvilliers demonstrated that cognitive flexibility was impaired in female, but not in male mice after administration of an orexin A receptor antagonist [55]. Since our study design did not include neurobiological measures and a gender-specific differentiation, our data cannot contribute to an estimation of the relevance of these animal data for research in humans. It remains to be a challenge for future human studies to investigate the relevance of orexin deficiency for selective cognitive dysfunctions related to narcolepsy.

Emotion processing

Our results demonstrate disturbances of cognitive processing of emotions in patients with narcolepsy, with simultaneously intact affective emotion processing (emotionalizing and fantasizing). Consistently, there were also no differences in objectively measured identification of positive, negative, and neutral facial expressions between narcoleptics and healthy subject. This is in line with a study by Pizza et al. who also did not report dysfunctions in perceiving and discriminating facial emotions in patients with narcolepsy type 1 [56]. It has been suggested that type 1 patients may use some kind of behavioral coping mechanism for the disturbances of cognitive emotion processing in the form of cataplexies triggered by emotions [22,23,57,58].

This assumption may at least partially explain our data since we also included narcolepsy type 2 patients in our study. These patients do not show cataplexy symptoms. An alternative explanation has been suggested by some authors, focusing the issue that it cannot be excluded that a brain physiological aberration related to orexin deficiency may lead to deviant emotion processing [1,59-62] for review see [58]. 10% of Narcolepsy type 2 shows at least some orexin deficiency [1], such that this alternative view does also not provide a robust explanation of our results. One may speculate the physiological changes in the brain, which are independent of orexin neuron loss, may induce deficient cognitive processing of emotions. Moreover, measures of orexin levels in the cerebrospinal fluid may help to accomplish mediator and moderator analyses for more differential approach to the detection of the role of orexin in altered emotion processing. Based on our current data, we can only state that aberrant emotion processing in patients with narcolepsy occurs independent of subjective daytime sleepiness.

Limitations

Some limitations of our study need to be addressed. Firstly, no separation of narcolepsy type 1 and type 2 was performed, because the sample size of the two groups was too small for adequate analyses and no gender-specific analyses were performed. Moreover, we only investigated subjective perception of sleepiness in this study. In future studies, objective physiological parameters of sleepiness should be assessed to verify or data on cognitive disturbances in patients with narcolepsy, which are independent of daytime sleepiness. The role of orexin deficiency also needs to be investigated more precisely with respect to the specificity of disturbed neuropsychological functions in patients with narcolepsy. Finally, the identified cognitive deficits should be examined with imaging techniques to gain a diversity of data concerning the possible etiology of the deficits.

Conclusion

In this study, we investigated neuropsychological impairments of patients with narcolepsy that occur independent of subjective daytime sleepiness and aging effects. Our data show, independently of subjective daytime sleepiness and age, only impaired tonic alertness, set-shifting, and cognitive processing of emotions in narcolepsy patients. We propose that comprehensive neuropsychological diagnostics and cognitive training interventions should be integrated into the clinical routines of the treatment of patients with narcolepsy. In parallel to medication of daytime sleepiness, neuropsychological training focusing on tonic alertness, set-shifting, and cognitive emotion processing can help to optimize cognitive performance of the patients. To further extend the scientific understanding of narcolepsy, we suggest that future neuroscience studies should specifically assess brain areas involved in tonic alertness, set-shifting, and the cognitive processing of emotions with neurobiological and neuroimaging methods. In particular, an investigation of orexin innervation and activity of the tyrosine hydroxylase in the LC could make an important contribution to the understanding of the neurobiological basis of the specificity cognitive dysfunctions occurring independently of daytime sleepiness in patients with narcolepsy.

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Conflicts of Interest

It is declared that there is no conflict of interest.

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