Sleep microstructure in Parkinson's disease related dementia: is cyclic alternating pattern a neurophysiological marker of neurodegeneration?

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INTRODUCTION AND METHODS

Sleep microstructure, specifically called cyclic alternating pattern or CAP, could be more informative than standard sleep stage scoring about neurophysiological alterations in neurodegenerative diseases. In fact, American Academy of Sleep Medicine criteria for sleep scoring are designed for healthy people and their use in patients affected by neurodegenerative diseases often result in not reliable sleep parameters and poor specific neurophysiologic markers. The main aim of this study was to evaluate CAP in PD patients with different degrees of cognitive impairment, in order to provide an objective measure of sleep microstructure alteration and evaluate possible associations with neurodegeneration progression.

Patients affected by PD with cognitive impairment were recruited at the Neurology Units of Hospital Auxologico Piancavallo of Verbania and C. Mondino Institute. PD diagnosis was based on Movement Disorder Society clinical diagnostic criteria. Patients underwent a complete neuropsychological test battery. Mild cognitive impairment (MCI) and dementia diagnosis were based on Movement Disorder Society task force guidelines. All patients underwent an in-lab full-night Videopolysomnography (PSG). CAP scoring of each patient was revised by an evaluator of the Sleep Medicine Unit of Parma. Exclusion criteria for both groups included moderate/severe depression or agitation not under control with psychoactive drugs, significant pain disturbances, an apnea-hypopnea index (AHI) > 15 per hour, a periodic limb movement index during sleep (PLMI) > 15 per hour.
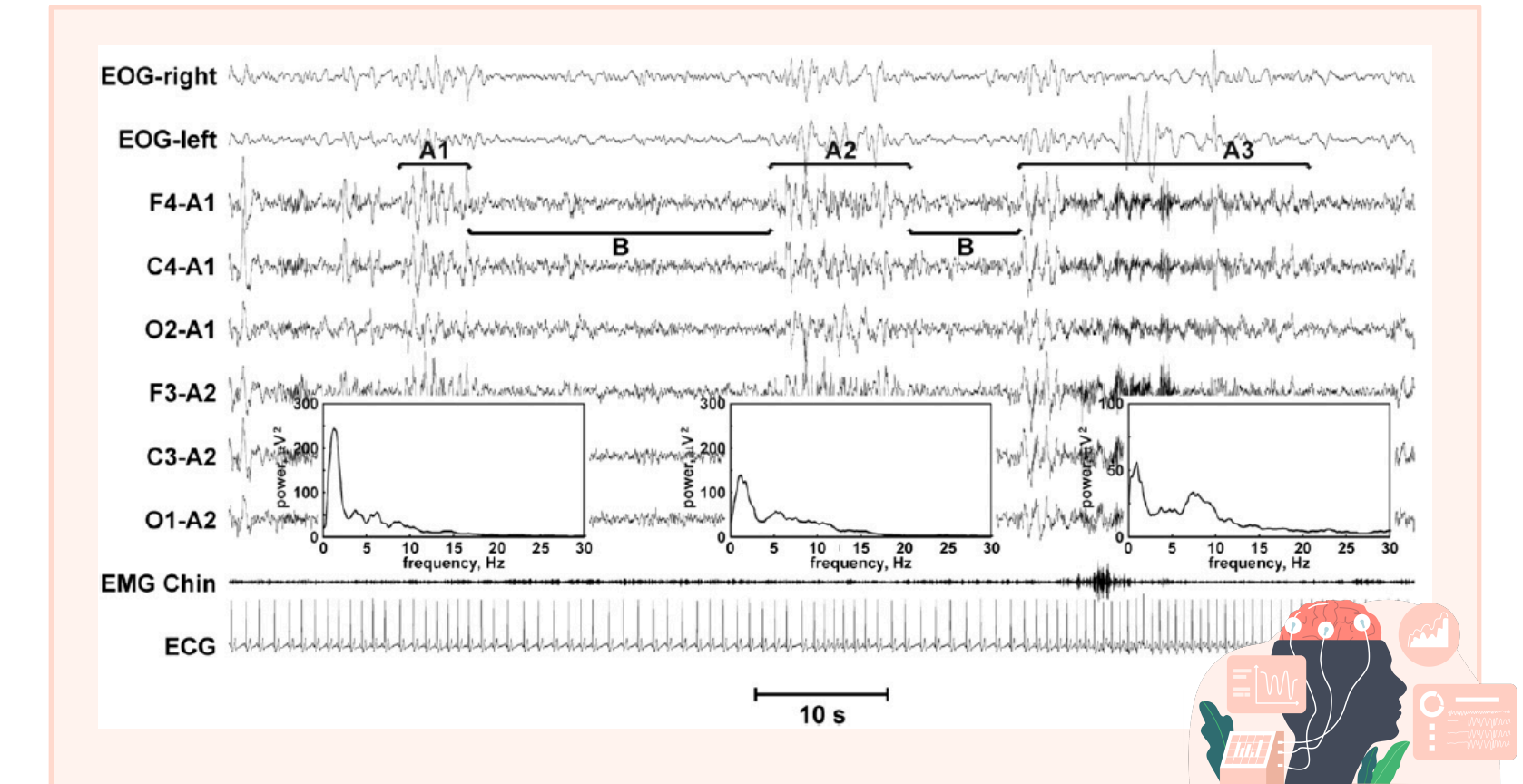
RESULTS

We recruited 16 PDMCI patients and 16 PDD patients, comparable for age and sex (**table 1**). Concerning sleep macrostructure both groups showed poor sleep efficiency and high standard deviations in sleep parameters. REM sleep (% of TST) was significantly reduced in PDD compared to PDMCI (p=0,002, **table 2**). CAP rate was significantly reduced in both groups compared to normative values, with a greater decrease in PDD compared to PDMCI (**table 3**). The proportion of CAP A1, A2 and A3 phases were reduced in both groups, and the same trend of reduction in PDD compared to PDMCI was found (**table 3**). Furthermore REM sleep time, CAP rate and related component A1, A2 and A3 phases correlated with both MMSEc and several neuropsychological tests (**table 4**). A Binomial logistic regression combining Total REM sleep time and CAP rate related to 1NREM has been built using two models to classify the two patients groups (**table 5-6**). CAP rate % 1 NREM contributed in improving the classification even with respect to accuracy (**figure 1**).

Table 1: Clinical and demographic features of PDMCI and PDD patients

	Group (0 PDD - 1 PDMCI)	N	Mean	Median	SD
Age (y)	PD-D	16	68.647	71	6.910
	PD-MCI	16	68.067	69	7.096
SEX (0 F - 1 M)	PD-D	16	M 7/17		
	PD-MCI	16	M 6/15		
Disease duration (years)	PD-D	16	7.800	8	4.074
	PD-MCI	16	10.133	9	6.739
MMSEc	PD-D	16	21.361	21.3	3.436
	PD-MCI	16	26.804	26.4	1.812
UPDRS III score	PD-D	16	31.000	34.0	8.246
	PD-MCI	16	25.200	25	10.178
Ldopa equivalent dose	PD-D	16	722.667	765	372.697
	PD-MCI	16	434.067	433	322.728

Table 2: Sleep macrostructure parameters in PDMCI and PDD patients

Group Descriptives

	Group	N	Mean	Median	SD	SE
Wake After Onset Sleep (min)	PDD	16	205.2	166.00	153.26	37.17
	PD MCI	16	213.0	199.80	123.5	31.88
Total Sleep Time (min)	PDD	16	400.9	413.00	188.86	45.81
	PD MCI	16	394.7	395.00	112.7	29.09
Sleep latency (min)	PDD	16	79.0	24.10	114.39	27.74
	PD MCI	16	75.9	4.20	152.7	39.42
Number Of Awakenings (n)	PDD	16	16.1	10.00	14.16	3.43
	PD MCI	16	23.6	23.00	15.4	3.99
Stage REM Latency from Sleep Onset	PDD	16	152.7	149.50	139.30	34.82
	PD MCI	16	167.7	122.00	113.9	29.41
SLEEP EFFICIENCY (%)	PDD	16	58.2	59.10	25.84	6.27
	PD MCI	16	60.5	65.30	15.4	3.97
STAGE N1 (%TST)	PDD	16	13.1	3.30	23.82	5.78
	PD MCI	16	14.2	7.40	17.7	4.56
STAGE N2 (%TST)	PDD	16	47.1	42.90	16.09	3.90
	PD MCI	16	55.5	47.60	36.4	9.39
STAGE N3 (%TST)	PDD	16	29.8	33.50	13.82	3.46
	PD MCI	16	28.9	23.70	19.9	5.15
STAGE REM (%TST) *	PDD	16	11.7	11.70	7.65	1.86
	PD MCI	16	24.3	25.50	12.9	3.33
RBD (n)	PDD	16	7 (43.7%)			
	PD MCI	16	4 (25%)			

* statistically significant (see Table 3)

Table 3: Sleep microstructure parameters in PD MCI and PDD patients: groups' descriptives

Group Descriptives

	Group	N	Mean	Median	SD	SE
CAP Rate (% N1 NREM) *	PD-D	17	3.765	1.60	5.12	1.241
	PD-MCI	15	11.673	4.600	15.775	4.073
CAPTime_NREM (minutes) all phases	PD-D	17	82.265	78.80	60.65	14.709
	PD-MCI	15	88.127	90.100	44.723	11.547
CAPcycles_NREM (number) all phases	PD-D	17	173.529	173.00	132.25	32.076
	PD-MCI	15	195.600	192.000	109.105	28.171
CAP Index (c/h) NREM all phases	PD-D	17	31.741	31.70	23.22	5.633
	PD-MCI	15	40.880	38.800	21.765	5.620
Cycle in sequence NREM (%) all phases	PD-D	17	82.947	92.80	25.22	6.117
	PD-MCI	15	89.367	93.300	11.096	2.865
CAP_Rate % NREM_phase A1	PD-D	17	15.971	12.90	12.36	2.997
	PD-MCI	15	17.500	13.600	9.621	2.484
CAP_Rate % NREM_phase A2	PD-D	17	5.729	4.60	5.01	1.214
	PD-MCI	15	6.160	4.500	3.768	0.973
CAP_Rate % NREM_phase A3	PD-D	17	3.465	2.80	2.82	0.683
	PD-MCI	15	6.820	5.100	7.700	1.988
CAP_Rate % N1_phaseA3 *	PD-D	17	1.971	0.00	3.66	0.889
	PD-MCI	15	9.127	0.700	14.338	3.702

* statistically significant (see Table 5)

Table 4: Correlations between neuropsychological tests and sleep microstructure

Correlation Matrix

		CAP_Rate % NREM_all phases	CAP_Rate % NREM_phase A1	CAP_Rate % NREM_phase A2	CAP_Rate % NREM_phase A3	MMSE	Verbal Span
CAP_Rate % NREM_all phases	Pearson's r	—					
	p-value	—					
CAP_Rate % NREM_phase A1	Pearson's r	0.902 ***	—				
	p-value	< .001	—				
CAP_Rate % NREM_phase A2	Pearson's r	0.888 ***	0.754 ***	—			
	p-value	< .001	< .001	—			
CAP_Rate % NREM_phase A3	Pearson's r	0.591 ***	0.216	0.454 **	—		
	p-value	< .001	0.234	0.009	—		
MMSE	Pearson's r	0.298	0.218	0.144	0.365 *	—	
	p-value	0.098	0.231	0.432	0.040	—	
Verbal Span	Pearson's r	0.037	-0.176	-0.014	0.455 *	0.446 *	—
	p-value	0.846	0.353	0.942	0.011	0.013	—
Raven Matrices	Pearson's r	0.459 *	0.274	0.463 **	0.498 **	0.549 **	0.450 *
	p-value	0.011	0.144	0.010	0.004	0.002	0.013

Note. * p < .05, ** p < .01, *** p < .001

**Table 5. Improvement of the model from 1 (%TST_REM) to 2 (%TST_REM + CAP Rate % N1).**

Model Fit Measures

Model	Deviance	AIC	BIC	R^2_{McF}	R^2_{CS}	R^2_N
1	34.0	38.0	41.0	0.231	0.273	0.364
2	31.7	37.7	42.1	0.284	0.325	0.434

Table 6. Binomial logistic regression measured by %TST_REM and CAP Rate % N1 with Group (PDMCI vs. PDD) as the dependent variable.

Model Coefficients - Group (0 PDD - 1 PDMCI)

Predictor	Estimate	SE	Z	p
Intercept	-2.6505	1.0183	-2.60	0.009
%TST_REM	0.1145	0.0468	2.45	0.014
CAP Rate % N1_all phases	0.0937	0.0739	1.27	0.205

Note. Estimates represent the log odds of "Group (0 PDD - 1 PDMCI) = PD-MCI" vs. "Group (0 PDD - 1 PDMCI) = PD-D"

Figure 1. Specificity vs. Sensitivity classifying the two groups (PDMCI vs. PDD) with REM sleep (%TST) and CAP Rate % N1 in model 2 as descripted in table 8 and 9.
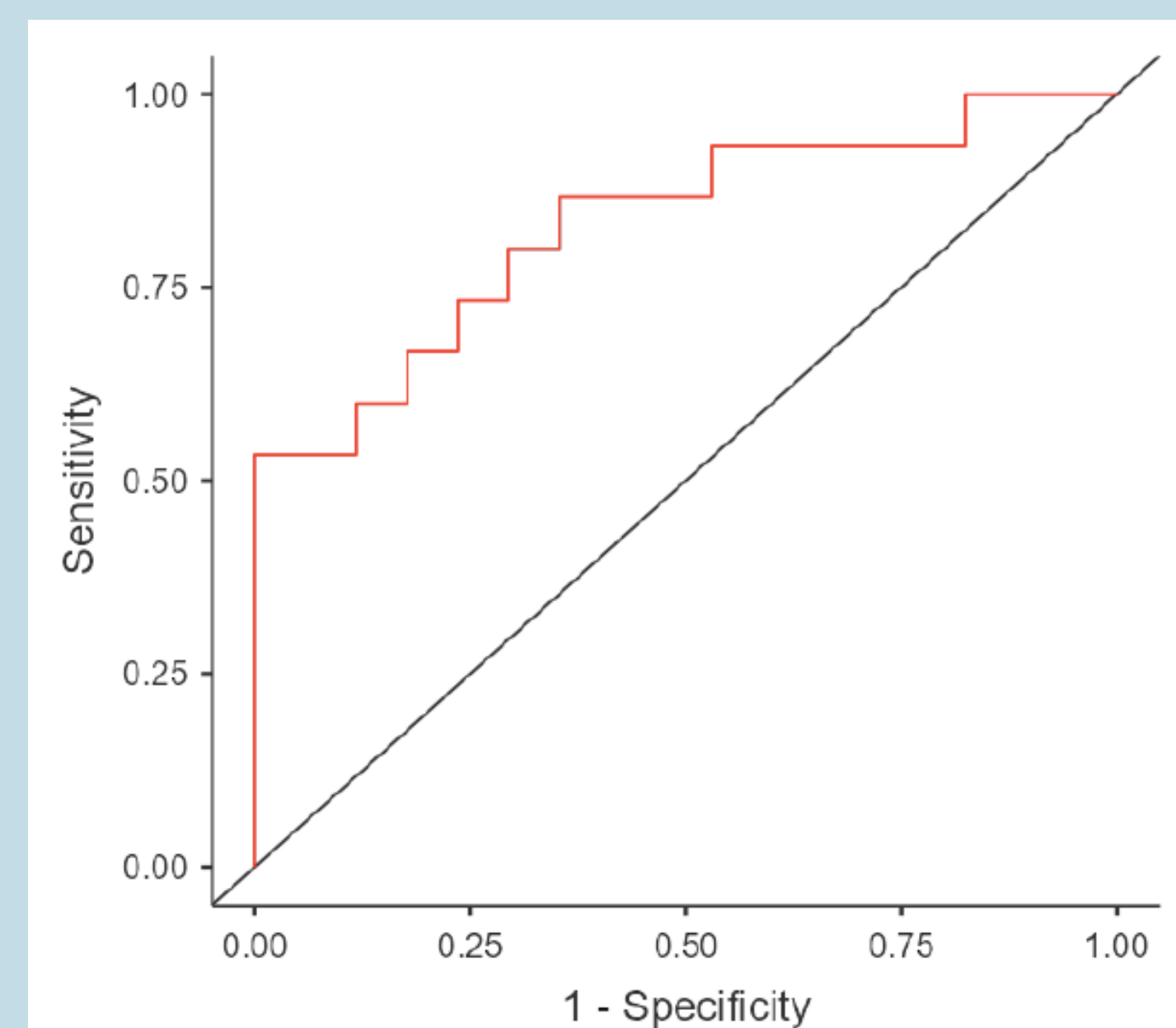
CONCLUSION

Combining sleep microstructure parameters and total REM sleep time seemed to give the best accuracy in predicting the degree of cognitive impairment. Despite the small sample size, sleep microstructure proved to add more information about neurodegeneration progression in PD related dementia. In this view, it could become a non-invasive and cost effective neurophysiological marker in neurodegenerative diseases.

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