Brain oscillatory patterns in mild cognitive impairment due to Alzheimer's and Parkinson's disease: An exploratory high-density EEG study

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HIGHLIGHTS

- Different brain oscillatory patterns characterize mild cognitive impairment due to Parkinson' s and Alzheimer's disease.
- Quantitative spectral EEG parameters can represent a surrogate biomarker of cognitive decline since its early stage.
- Quantitative spectral analysis of EEG signals could provide support in monitoring disease progression.

ABSTRACT

Objective: We investigated brain cortical activity alterations, using a resting-state 256-channel high-density EEG (hd-EEG), in Alzheimer's (AD) and Parkinson's (PD) disease subjects with mild cognitive impairment (MCI) and correlations between quantitative spectral EEG parameters and the global cognitive status assessed by Montreal Cognitive Assessment (MoCA) score.
Methods: Fifteen AD-MCI, eleven PD-MCI and ten age-matched healthy-controls (HC) underwent hd-EEG recordings and neuropsychological assessment. Cerebrospinal fluid biomarker analysis was performed to obtain well-characterized groups. EEG spectral features were extracted and the differences between the three groups, as well as correlations with MoCA, were investigated.
Results: The results showed significantly lower alpha2 power and alpha2/alpha1 ratio in both AD-MCI and PD-MCI compared to controls. The significantly higher theta and lower beta power and alpha/theta ratio were observed in PD-MCI compared to AD-MCI and HC. MoCA score correlated inversely with theta power and directly with alpha2 and beta powers, as well as with alpha2/alpha1 and alpha/theta ratios.
Conclusions: This study highlighted significant differences in EEG patterns in AD-MCI and PD-MCI patients and remarked the role of EEG parameters as possible surrogate markers of cognitive status in both neurodegenerative diseases.
Significance: In addition to well-established biomarkers, our findings could support early detection of cognitive dysfunction in neurodegenerative disorders and could help to monitor disease progression and therapeutic responses.

1. Introduction

Mild cognitive impairment (MCI) can be a common early clinical condition in both Alzheimer's Disease (AD) and Parkinson's Disease (PD) (Fonseca et al., 2013). Cognitive dysfunction is a relevant research focus in AD and PD: while the main expression of AD is dementia, PD is frequently accompanied by cognitive dysfunction,

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ranging from a state of Mild Cognitive Impairment to dementia (Goldman et al., 2015). Among the wide spectrum of PD non-motor symptoms, cognitive impairment is the most common: MCI affects up to 50% of non-demented PD patients and about 30% of newly diagnosed patients, representing an important risk factor of progression to dementia (Litvan et al., 2012, Monastero et al., 2018).

While the diagnosis of probable AD could be formulated since from the preclinical stages of the disease through cerebrospinal fluid (CSF) and molecular imaging biomarkers, there is a growing interest in the research of biomarkers which can be used to identify and characterize the early cognitive impairment associated to PD (Goldman et al., 2015). Although differential diagnosis between the two neurodegenerative diseases is not clinically challenging, the deep comprehension of distinctive and overlapping mechanisms of cognitive impairment is extremely important in order to achieve an earlier diagnosis, to develop a phenotype-based prognostic assessment and to detect new targets for disease-modifying therapy development. According to literature, the pathological substrate at the basis of cognitive impairment spectrum in PD is actually extremely heterogeneous, including the presence of Lewy body pathology, AD-like neuropathological alterations and cerebrovascular impairment (Delgado-Alvarado et al., 2016, Jellinger et al., 2010).

There is a growing research interest towards quantitive spectral EEG parameters as potential biomarkers to characterize cognitive impairment in different disorders (Fonseca et al., 2009, Rho et al., 2011) since from the early stages, reflecting the underlying synaptic dysfunction which could be related to different neuropathological alterations. The spectral EEG parameters may complement neurophysiological testing for studying cognitive decline in patients with neurodegenerative disorders (Klassen et al., 2011) and, thus, it might be useful to support the differential diagnosis. EEG in patients suffering from cognitive impairment due to probable AD is generally characterized by a shift of the power spectra to lower frequencies (Dauwels et al., 2010, Jeong et al., 2004, Mazzon et al., 2018). Similar deterioration of brain oscillatory activity associated with cognitive decline was reported also in patients with Parksinson's disease (Caviness et al., 2016, Fonseca et al., 2009, Bousleiman et al., 2014). A higher EEG slowing was observed in PD patients with dementia (PDD) compared to advanced stage AD patients (Babiloni et al., 2011, Fonseca et al., 2013). However, there are only few comparative studies between AD and PD, performed in different stages of cognitive decline, based on different analysis techniques applied on a limited number of EEG channels, and reporting non-consistent results. Therefore, brain oscillatory pattern differences between these two neurodegenerative disorders, the capability of EEG based biomarkers to discriminate between AD and PD at the MCI stage and the correlation between EEG with the extent of cognitive decline are still debated (Caviness et al., 2016).

The main aim of this exploratory study was to investigate EEG spectral parameters differences between AD-MCI, PD-MCI and age-matched healthy subjects, using a 256-channel high-density EEG. In addition, we investigated the correlations between quantitative spectral EEG parameters and the global cognitive status assessed by Montreal Cognitive Assessment (MoCA) test.

2. Materials and Methods

2.1. Study population

Out of 35 patients enrolled at the Neurological Clinic of Trieste University Hospital the study was conducted on 26 patients (15 AD-MCI and 11 PD-MCI) who fulfilled the inclusion and exclusion criteria. The study also included 10 healthy controls (HC).

In particular, the 15 AD-MCI patients included had a confirmed clinical diagnosis of MCI due to possible AD dementia with evidence of the AD pathophysiological process, according to NIA-AA criteria (Frisoni et al., 2011). All AD-MCI patients were receiving treatment with AChE inhibitors during the study period, except one due to cardiovascular contraindication. Eleven PD-MCI patients with a clinical diagnosis of PD according to MDS-PD Clinical Diagnostic Criteria (Postuma et al, 2015) and who met level II Movement Disorder Society (MDS) Task Force guidelines (Litvan et al., 2012) were also included. All PD-MCI patients were using levodopa and underwent neuropsychological evaluation and EEG recording in "on" motor state. Control group encompassed 10 healthy subjects with no reported health problems and with a neuropsychological examination score within normal range. HC were matched to both pathological groups according to education, age and gender. Clinical and demographic characteristics of enrolled AD-MCI, PD-MCI and HC subjects are reported in Table 1.

Patients with a diagnosis of dementia according to the Clinical Dementia Rating (Morris et al., 1993), with severe neurological and/or psychiatric conditions and with comorbidities implying significant reduction in life expectancy were excluded from the study. Treatment with drugs able to influence EEG signals (antiepileptic, anti-psychotic drugs), except for short-time benzodiazepines intake far from EEG recording, were considered as additional exclusion criteria. Nine out of 35 patients were excluded from the study because of the presence of exclusion criteria: 4 patients were taking drugs capable to influence EEG signals, such as antipsychotic and antiepileptic drugs; 3 patients suffered from other parkinsonian syndromes and the last 2 patients had a diagnosis of depression.

All included participants underwent high-density EEG acquisition, clinical and neuropsychological assessment. The study was approved by the Local Ethics Committee CEUR (Comitato Etico Unico Regionale, FVG, Italy) with approval number 95/2018. All participants released their informed consent to participate in the study. The research was conducted in line with the principles of the Declaration of Helsinki.

2.2. Clinical and neuropsychological assessment

All patients underwent a comprehensive clinical-neurological, laboratory and instrumental assessment including a brain imaging, an extensive neuropsychological evaluation, Clinical Dementia Rating (CDR), Activities of Daily Living (ADLs) and Instrumental activities of Daily Living (IADLs) assessment, blood tests, a lumbar puncture for the research of CSF biomarkers of AD-type dementia and an EEG recording. Diagnosis of PD-MCI was made according to the Movement Disorder Society Task Force guidelines. Level I neuropsychological evaluation was performed using the Montreal Cognitive Assessment (MoCA) for its higher sensitivity compared to Mini Mental State Examination (MMSE), particularly in exploring executive functions. Level II extensive neuropsychological assessment was performed by a specialized neuropsychologist and included test to explore the following five cognitive domains: attention, executive functions, visuospatial functions, episodic memory and language.

PD patients' motor disability was scored by the modified Hoehn and Yahr staging scale (Goetz et al., 2004) and PD severity was evaluated in accordance with the Unified Parkinson Disease Rating Scale – Motor Examination (UPDRS III) and Hoehn and Yahr (H&Y). Overall daily dosage of dopaminergic drugs was calculated using the Levodopa Equivalent Daily Dosage (LEDD).

Table 1
Clinical and demographic characteristics of enrolled AD-MCI, PD-MCI and HC subjects.

	HC	AD-MCI	PD-MCI	MCI tot	AD vs HC (adj. p-value)	PD vs HC (adj. p-value)	AD vs PD (adj. p-value)
N	10	15	11	26	-	-	-
Sex (M/F)	6/4	9/6	8/3	17/9	n.s.	n.s.	n.s.
Age (yr)	70.40 ± 5.27	73.60 ± 5.15	74.82 ± 8.35	74.12 ± 6.57	n.s.	n.s.	n.s.
Education (yr)	14.50 (8–19)	8.00 (6–18)	13.00 (8–19)	12.50 (6–19)	n.s.	n.s.	n.s.
Disease duration (yr)	-	4.47 ± 2.95	6.00 ± 5.66	5.12 ± 0.84	-	-	n.s.
MoCA	28.90 ± 0.88	22.80 ± 2.96	22.00 ± 3.19	22.46 ± 3.02	<0.001	<0.001	n.s.
CSF biomarkers							
Aβ-42 (pg/mL)	-	427 (66–1045)	791 (199–1634)	-	-	-	n.s.
T-Tau (pg/mL)	-	440 (276–1195)	237 (119–754)	-	-	-	0.004
p-Tau (pg/mL)	-	67.64 (39.60–281.00)	37.40 (15.70–63.30)	-	-	-	<0.001
T-Tau/Aβ2	-	1.00 (0.58–5.37)	0.30 (0.20–0.87)	-	-	-	<0.001

HC: healthy controls. AD-MCI: Alzheimer's disease-mild cognitive impairment. PD-MCI: Parkinson's disease-mild cognitive impairment. MoCA: Montreal Cognitive Assessment. CSF: cerebrospinal fluid. n.s.: not significant.

2.3. High-density EEG acquisition and processing

All study participants underwent an eye-closed resting-state 20 minutes EEG recordings. EEG signals were collected with the 256 channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene OR, USA) and using the Net Amps 300, a high-input impedance amplifier (Electrical Geodesics Inc., Eugene OR, USA) with a 256 Hz sampling rate. The exam was conducted in a silent and low intensity lighting environment to induce patient relaxation. Patients were instructed to relax, but to stay awake and to minimize eye and body movements. During the data acquisition process, the tracings were monitored online by a neurologist to verify patients' vigilance and the appearance of artifacts. If somnolence signs appeared, patients were stimulated to restore waking state. During the whole time of recording, patients underwent also some stimulation such as eye opening and closure, to maintain awake condition. All impedances were measured, and kept below 50 kΩ. The tracings were visually inspected by an expert neurologist for the detection of artifacts and signs of sleep and drowsiness, and if present they were rejected. The first continuous artefact-free 120 seconds were selected for analysis. All channels were digitally filtered with the 0.5–35 Hz 2nd order bandpass filter and were re-referenced to a common average reference. Power spectral density (PSD) was calculated using scripts developed in MATLAB (MathWorks Inc., Natick, MA) on 120 s artifact free epochs for each channel using Welch's periodogram (50% overlap between 10-s Hamming windowed segments). Beside for the artifacts the selected epochs were visually inspected for signs of sleep and drowsiness.

The relative power of the following spectral bands and sub-bands were calculated from PSD: delta (2–4 Hz), theta (4–8 Hz), $alpha_1$ (8–10.5 Hz), $alpha_2$ (10.5–13 Hz), $beta_1$ (13–20 Hz), $beta_2$ (20–30 Hz), for each channel. The relative power for each frequency band was calculated as a ratio between the absolute power of that frequency band and the total power from 2 to 30 Hz. In addition, also α_2/α_1 and α/θ spectral ratios were extracted. Relative power for each band, sub-band, α_2/α_1 and α/θ parameters were averaged over all 256 electrodes, as well as over specific areas, namely frontal, central, parietal, temporal and occipital areas, averaging over corresponding channels to perform regional analysis.

2.4. Statistical analysis

Statistical analysis was performed by using SPSS Statistics 21.0 software. Continuous variables with a normal distribution are presented as mean and standard deviation (SD), those with a skewed distribution as median and range, and categorical variables as counts. Differences in EEG parameters between AD-MCI, PD-MCI and HC groups were investigated. The differences between three groups were investigated using ANOVA for parametric data or Kruskall-Wallis test for non-parametric data and post-hoc tests were performed to assess pairwise group differences. The p-values were adjusted with Bonferroni correction for multiple comparison between three considered groups. Correlations between MoCA test score and extracted quantitative spectral EEG parameters were also investigated. In the testing of the statistical significance of correlation coefficients we adjusted p-values with the stringent Bonferroni correction to maintain the total type I error rate at a sufficiently low level. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Clinical and demographic data

Table 1 reports the clinical and demographic data of included AD-MCI and PD-MCI patients, as well as of healthy controls. No significant differences in age, education and sex were observed between three groups. There were also no significant differences in disease duration and MoCA test results between AD-MCI and PD-MCI patients. The mean MoCA score in healthy controls (28.90 ± 0.88) was significantly higher compared to AD-MCI and PD-MCI patients.

Regarding the motor deficit and disease severity of included PD-MCI patients, mean UPDRS III score was 36.0 ± 11.1 and median (range) Hoehn and Yahr stage was 2 (2–4). The median (range) of LEDD was 450 (260–1140). Sixty-four percent of PD-MCI patients were classified as multi-domain amnestic MCI (aMCImd), while 27% and 9% presented a single-domain non-amnestic MCI (naMCIsd) and multi-domain non-amnestic MCI (naMCImd), respectively. No patients showed a single-domain amnestic MCI (aMCIsd).

3.2. EEG analysis

In Table 2 median (range) values of the calculated EEG parameters in AD-MCI, PD-MCI and HC groups, as well as the results of comparison between three groups are reported.

Relative $alpha_2$ power and $alpha_2/alpha_1$ ratio were significantly lower in PD-MCI and AD-MCI groups compared to HC, whereas no significant differences were observed for these spectral parameters between these two pathological groups. In addition, the relative $alpha_1$ sub-band power was significantly higher in AD-MCI than in HC group. No significant differences for relative alpha band power were found between three groups. Relative $beta_1$ power resulted significantly lower in PD-MCI than HC, while

Table 2
Median (range) values of extracted EEG parameters for AD-MCI, PD-MCI and HC and comparison between three groups.

	AD-MCI (n = 15)	PD-MCI (n = 11)	HC (n = 10)	(p-value)	AD vs HC (adj. p-value)	PD vs HC (adj. p-value)	AD vs PD (adj. p-value)
δ	0.13 (0.10–0.27)	0.19 (0.07–0.33)	0.17 (0.12–0.22)	0.787	-	-	-
θ	0.21 (0.10–0.33)	0.40 (0.26–0.48)	0.16 (0.12–0.20)	**<0.001**	0.248	**<0.001**	**0.004**
α	0.30 (0.14–0.51)	0.22 (0.15–0.41)	0.28 (0.22–0.47)	0.214	-	-	-
β	0.26 (0.14–0.45)	0.15 (0.06–0.31)	0.29 (0.21–0.45)	**<0.001**	0.224	**<0.001**	**0.040**
α_1	0.22 (0.09–0.42)	0.16 (0.11–0.36)	0.13 (0.10–0.22)	**0.022**	**0.018**	0.615	0.462
α_2	0.08 (0.04–0.18)	0.05 (0.03–0.12)	0.15 (0.11–0.24)	**<0.001**	**0.009**	**<0.001**	0.246
β_1	0.14 (0.08–0.27)	0.10 (0.04–0.16)	0.16 (0.13–0.26)	**0.003**	0.265	**0.002**	0.125
β_2	0.11 (0.05–0.19)	0.05 (0.02–0.15)	0.13 (0.07–0.22)	**0.001**	1.000	**0.002**	**0.010**
α/θ	1.37 (0.44–4.90)	0.55 (0.33–2.14)	1.85 (1.30–3.86)	**0.003**	0.855	**0.003**	**0.039**
α_2/α_1	0.39 (0.15–0.83)	0.32 (0.17–0.68)	1.14 (0.81–1.56)	**<0.001**	**<0.001**	**<0.001**	0.827

Note. Relative delta – δ, theta – θ, alpha – α, beta – β, $alpha_1$ - α_1, $alpha_2$ - α_2, $beta_1$ - β_1 and $beta_2$ - β_2 powers; alpha-to-theta ratio - α/θ, $alpha_2$-to-$alpha_1$ ratio - α_2/α_1. HC: healthy controls. AD-MCI: Alzheimer's disease-mild cognitive impairment. PD-MCI: Parkinson's disease-mild cognitive impairment. p-values were adjusted (adj. p-values) with Bonferroni correction for multiple comparison between three considered groups.

relative beta and $beta_2$ power showed lower values in PD-MCI than both AD-MCI and HC. Relative theta power was significantly higher in PD-MCI than in AD-MCI and HC, while alpha/theta ratio was found significantly lower in PD-MCI than AD-MCI and HC. No significant differences for relative delta power were observed between three groups.

The differences in EEG spectral patterns between AD-MCI, PD-MCI and healthy subjects can be also observed on average EEG topographic maps of calculated spectral parameters (Fig. 1).

Regional sub-analysis highlighted that the observed global alterations and differences between three groups found for relative theta, beta, $alpha_1$, $alpha_2$ powers and $alpha_2/alpha_1$ ratio were observed in all areas. Alpha/theta ratio was also significantly lower in PD-MCI than AD-MCI in all regions, except temporal regions. No significant differences between groups in any of the considered areas were observed for relative delta and total alpha power. In addition to aforementioned globally diffused differences detected in all areas, a significantly lower relative beta power was found in the PD-MCI compared to AD-MCI in the frontal, parietal, right temporal and occipital regions (adj. p = 0.009; adj. p = 0.048; adj. p = 0.033 and adj. p = 0.035, respectively). Furthermore, regional analysis showed significant differences in theta and beta relative powers between AD-MCI and HC in temporal areas. In particular, higher relative theta power in the right temporal region (adj. p = 0.047), lower relative beta power in the occipital and right temporal areas (adj. p = 0.032 and adj. p = 0.049, respectively) and lower relative $beta_1$ sub-band power in the left temporal region (adj. p = 0.037) were observed in AD-MCI compared to HC.

3.3. Correlation between EEG parameters and cognitive deficit

The overall cognitive deficit measured with MoCA score correlated inversely with relative theta power (*Spearman's* ρ = -0.61; adj. p < 0.001), while positive significant correlations with relative $alpha_2$, beta and $beta_2$ powers (*Spearman's* ρ = 0.56, adj. p < 0.001; *Spearman's* ρ = 0.58, adj. p < 0.001 and *Spearman's* ρ = 0.66, adj. p < 0.001, respectively) were observed. In addition, MoCA scores correlated significantly with alpha/theta and alpha2/alpha1 ratios (*Spearman's* ρ = 0.55; adj. p < 0.001 and *Spearman's* ρ = 0.55; adj. p < 0.001, respectively). No significant correlations between the extracted EEG parameters and the age, education and disease duration were detected.

4. Discussion

The main finding of this exploratory study is the identification of different EEG spectral patterns between AD-MCI, PD-MCI and healthy controls, as well as the correlations between quantitative spectral EEG parameters and the global cognitive status assessed by Montreal Cognitive Assessment (MoCA) test.

In particular, the present study highlighted significant differences in the alpha rhythm sub-bands, showing a reduction of $alpha_2$ power (alpha-high) with a consequent lower $alpha_2/alpha_1$ ratio in both pathological groups compared to HC, with no significant differences in the total alpha power band. This finding could be related to a process of power redistribution within alpha rhythm, highlighting a shift towards the lower alpha sub-band (8–10.5 Hz) in both neurodegenerative disorders. The observed trend is consistent to the data reported in previous studies (Dauwels et al., 2010, Babiloni et al., 2015, He et al., 2017, Guner et al., 2017) showing the presence of a global EEG slowing related to cognitive impairment. Studies performed with different techniques (M/EEG, EEG source analysis with eLORETA) demonstrated a global background rhythm slowing, both in AD and in PD with cognitive impairment (Babiloni et al., 2011, Vecchio et al., 2013, Cozac et al., 2016). Furthermore a study about cortical sources analysis conducted by Babiloni et al. (Babiloni et al., 2018) analysing alpha rhythm sub-bands, demonstrated the presence of a higher functional connectivity between posterior cortical high-alpha sources in cognitively intact subjects, while a substantial reduction of inter-hemispheric connectivity of high-alpha sources was reported in both AD-MCI and PD-MCI patients, with no significant differences in alpha sources connectivity between the two pathological groups.

Alpha rhythm is the dominant frequency during relaxed waking state and the choice to investigate alpha rhythm sub-bands was due to the hypothesis that these sub-bands could reflect different functional aspects: low-frequency alpha could indicate the synchronization of diffuse neural networks, mainly related to subject's attentive state fluctuations, while upper alpha band would reflect the oscillation of specific neural systems involved in more selective cognitive processes for elaboration of semantic or sensorimotor information (Babiloni et al., 2017). Considering these assumptions, our results suggest that the reduction of $alpha_2/alpha_1$ ratio in both pathological groups compared to HC, might represent a typical oscillatory pattern of neurodegeneration since a pre-dementia stage, highlighting the presence of plenty of shared mechanisms as common neural bases for cognitive impairment, including the interference of misfolded proteins with synaptic transmission and with networks functionality. Moreover, the selection of AD patients according to NIA-AA criteria for probable AD with the evidence of the physio-pathological process leads support to data reliability.

Our findings also support the concept that patients affected by AD and PD with cognitive impairment could share a similar neurophysiologic mechanism causing the lowering of alpha power called "cortical disconnection syndrome", even at a prodromal stage of

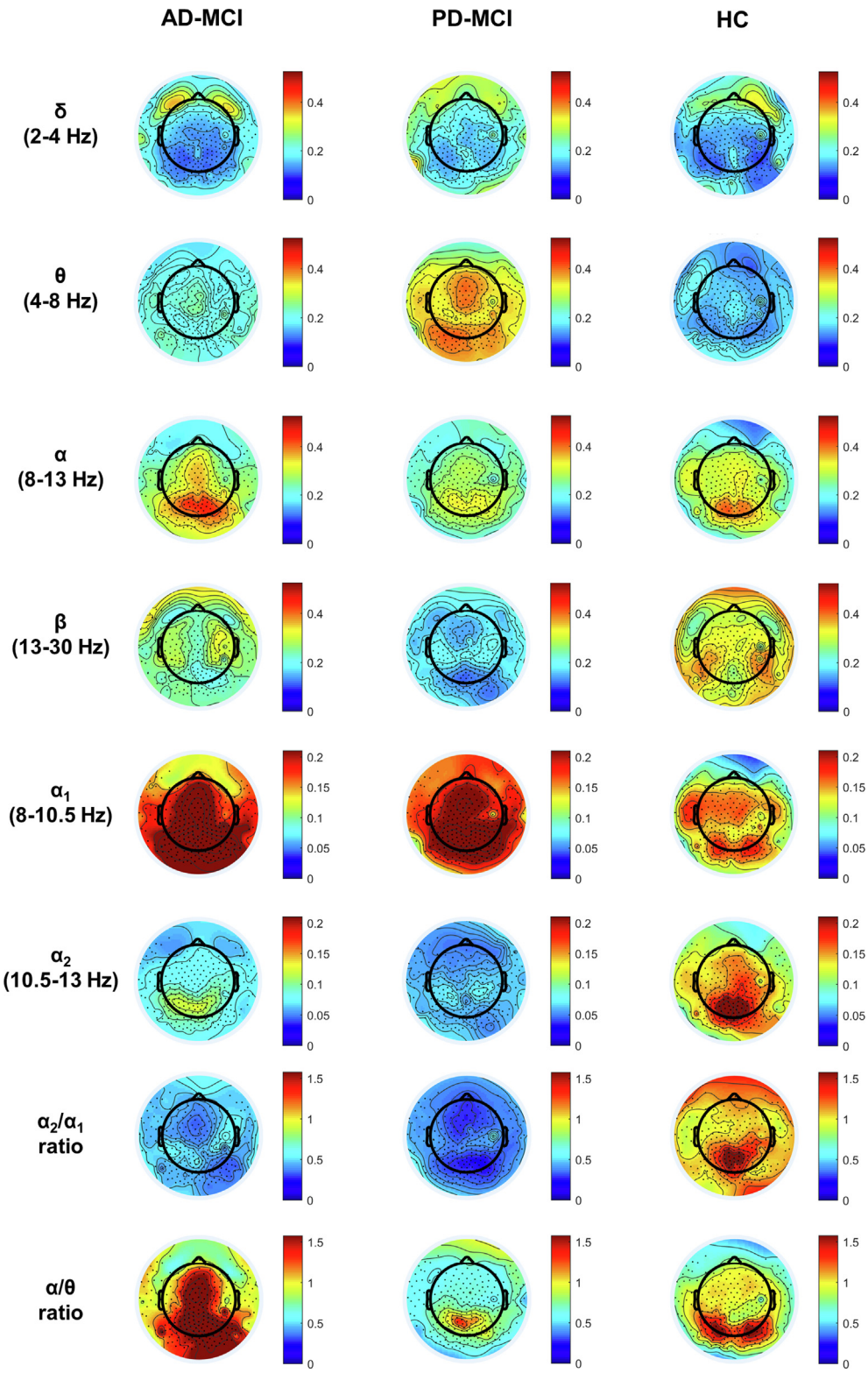

Fig. 1. Average EEG topographic maps of calculated spectral parameters for each group (AD-MCI, PD-MCI and HC). Relative delta – δ, theta – θ, alpha – α, beta – β, alpha1 - α1, alpha2 - α2, alpha-to-theta ratio - α/θ, alpha2-to-alpha1 ratio - α2/α1; AD-MCI: Alzheimer's disease-mild cognitive impairment. PD-MCI: Parkinson's disease-mild cognitive impairment. HC: healthy controls.

MCI (Bohnen et al., 2015). Noteworthy, high-alpha power reduction did not discriminate between AD-MCI and PD-MCI patients: this finding suggests that cholinergic ascending systems are impaired in both groups and that the degeneration of these pathways might play a significant role in the modulation of cortical oscillations, keeping the integrity of global alpha rhythm in both neurodegenerative diseases (Babiloni et al., 2018). Other studies reported a reduction of alpha band cortical sources (low and high alpha) higher in AD patients than in PDD (AD > PDD > HC) (Babiloni et al., 2011, Babiloni et al., 2018). Our results, as above-

mentioned, did not show significant differences in alpha power between AD and PD patients; these data might be correlated to an earlier disease stage of our AD population: probably in a dementia stage a further shift towards low alpha frequencies might be hypothesized.

Another relevant finding of this study is the significant increase in the theta power and the significant reduction in the beta band characterizing the PD-MCI group compared to both AD-MCI and HC. A concomitant significant reduction of alpha/theta ratio in the PD-MCI group was observed compared to AD-MCI and HC. The finding of an increase in the theta power and a reduction in the beta band in PD-MCI patients was previously described in PD patients with dementia (Babiloni et al., 2011, Fonseca et al., 2013), but not in an early stage of MCI. Moreover, the increased delta power reported in previous PDD studies (Babiloni et al., 2011, Fonseca et al., 2013) was not found in the present study, probably due to the milder stage of cognitive impairment of our patients.

It has been suggested that the higher slowing down of the EEG frequency in PD with cognitive impairment compared to AD is linked to impaired interactions between thalamic and cortical structures, leading to a "subcortical-cortical disconnection syndrome"; the increase of slow frequencies power could be also related to the cholinergic dysfunction present in PD-MCI (Bosboom et al., 2009). Previous studies have shown that a long-term treatment with acetylcholinesterase inhibitors was able to reverse the enhancement of resting slow rhythms and to improve cognitive status in responders, both in AD and PD patients (Bosboom et al., 2006, Moretti et al., 2007, Farlow et al., 2000). In our study, there was no significant difference between AD-MCI group and HC in the theta band power, although according to literature more pronounced EEG slowing could be expected in these patients (Miyauchi et al., 1994, Chiaramonti et al., 1997). It should also be underlined that in the present study all included AD patients, except one, were receiving AchE inhibitors treatment, so that EEG rhythms could have been influenced. The increase of theta power has been also reported in studies comparing PD with normal cognition (PD-N), PD-MCI and PDD, showing higher theta band power in PD-MCI compared to PD-N, leading support to the hypothesis that this EEG abnormality might represent an early marker of cognitive impairment in PD (He et al., 2017, Mostile et al., 2019). Chaturvedi et al. proposed the alpha1/theta ratio as a parameter able to distinguish PD patients (with and without cognitive impairment) from healthy controls (Chaturvedi et al., 2017). Confirming this result, our study suggests to broaden the potential role of the alpha/theta ratio as a marker of cognitive impairment, not only to distinguish PD from HC, but also to differentiate PD-MCI from AD-MCI.

Moreover, regional analysis confirmed the global diffusion of EEG parameters alterations concerning theta, beta, $alpha_1$, $alpha_2$ frequency bands. In addition, regional analysis also highlighted a significant difference in the theta and beta band powers between AD-MCI group and HC, with enhanced theta power in AD-MCI localized in the right temporal region, together with a reduction of the beta power in the occipital and both temporal areas, compared to healthy controls. These data show the presence of a possible pattern of EEG slowing involving temporal and occipital regions that could be primarily affected in the early stage of AD. Finally, relative power of the beta band resulted significantly lower in PD-MCI compared to AD-MCI in the frontal, parietal, right temporal and occipital regions, with a difference more pronounced in the frontal area. This finding might be related to cortical motor networks involvement and executive functions impairment in PD patients (Kamei et al., 2010, Boon et al., 2019).

EEG based biomarkers may be useful for the screening of global cognitive decline in elderly individuals (Choi et al., 2019) and has shown potential in identifying the earliest signs of brain dysfunction in subjects with mild cognitive impairment or dementia (Jackson and Snyder, 2008). Our results showed that the identified EEG parameters are informative and should be furtherly investigated together with other pathology related biomarkers in a larger study sample to produce predictive diagnostic models able to improve differential diagnosis of different disorders in the early stages of cognitive decline.

In addition, there is a growing research interest in neurophysiological biomarkers for monitoring neurological disability progression, usually measured by clinical scales (Geraedts et al, 2018, He et al., 2017, Vecchio et al., 2013, Mazzon et al., 2019, Ajčević et al., 2021a, 2021b, Choi et al, 2019). Our study also aimed to investigate whether quantitative spectral EEG parameters were related to overall cognitive performance, measured by MoCA test, in AD-MCI and PD-MCI patients including also healthy controls. Relative beta, $beta_2$ and $alpha_2$ powers correlated positively with the MoCA score, while a significant negative correlation between relative theta power and the MoCA score was detected. Our findings are consistent with previous studies reporting EEG slowing as a valid surrogate marker for cognitive decline in both AD and PD patients (Vecchio et al., 2013, Cozac et al., 2016, Babiloni et al., 2006). These previous studies were mainly based on the MMSE for the cognitive assessment, while we used MoCA test for its higher sensitivity in detecting cognitive impairment especially in MCI. Furthermore, MoCA test is considered more sensitive compared to MMSE in the assessment of the executive functions, that might be frequently impaired in PD (Nasreddine et al., 2005).

Despite some limitations such as the small sample size, one of the advantages of the present study is the comparison of demographically well matched groups of AD and PD patients at an early stage of cognitive impairment with a HC group. Furthermore, the fulfilling of a CSF-biomarkers based diagnosis and the execution of an extensive neuropsychological assessment in our sample increased results reliability and gave more strength to the results obtained. Concernig cognitive assessment we followed Litvan et al. guidelines proposing a distinction in the diagnostic flowchart, in which Level I is an abbreviated assessment able to identify the presence of PD-MCI, while Level II consists of an extensive assessment that explores more cognitive domains, offering higher diagnostic certainty (Litvan et al., 2012). Noteworthy, the above mentioned findings were obtained performing a non-invasive technique, such as quantitative electroencephalography, strengthened by the high spatial resolution of the high-density EEG acquisition system.

5. Conclusions

This exploratory study highlighted significant differences in the EEG spectral patterns in AD and PD patients during the very early stage of cognitive impairment, identifying distinctive oscillatory patterns characterized by reduced $alpha_2$ power and $alpha_2/alpha_1$ ratio in both AD-MCI and PD-MCI compared to controls and by a predominance of theta activity and a lowering of beta power in PD-MCI compared to AD-MCI and controls. These results underline the presence of a power redistribution within alpha rhythm consisting of a shift towards lower alpha frequencies in both neurodegenerative disorders and the occurring of a higher EEG slowing in PD compared to AD patients, probably related to cortico-subcortical connections disruption together with cholinergic pathways impairment implied in PD-MCI pathogenesis. Our results widen the knowledge on oscillatory patterns in these neurodegenerative disorders, useful also for formulation of hypothesis for future research.

The identified correlations between EEG parameters and MoCA score remark their possible role as surrogate markers of cognitive status in both neurodegenerative diseases. Our results together with further biomarker-based studies are extremely important to achieve an early detection of cognitive dysfunction in both neurodegenerative disorders, providing support to clinical practice especially in monitoring disease progression and therapeutic responses.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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