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Poor reactivity of posterior electroencephalographic alpha rhythms during the eyes open condition in patients with dementia due to Parkinson's disease

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ABSTRACT

Here, we hypothesized that the reactivity of posterior resting-state electroencephalographic (rsEEG) alpha rhythms during the transition from eyes-closed to -open condition might be lower in patients with Parkinson's disease dementia (PDD) than in patients with Alzheimer's disease dementia (ADD). A Eurasian database provided clinical-demographic-rsEEG datasets in 73 PDD patients, 35 ADD patients, and 25 matched cognitively unimpaired (Healthy) persons. The eLORETA freeware was used to estimate cortical rsEEG sources. Results showed substantial (greater than −10%) reduction (reactivity) in the posterior alpha source activities from the eyes-closed to the eyes-open condition in 88% of the Healthy seniors, 57% of the ADD patients, and only 35% of the PDD patients. In these alpha-reactive participants, there was lower reactivity in the parietal alpha source activities in the PDD group than in the healthy control seniors and the ADD patients. These results suggest that PDD patients show poor reactivity of mechanisms desynchronizing posterior rsEEG alpha rhythms in response to visual inputs. That neurophysiological biomarker may provide an endpoint for (non) pharmacological interventions for improving vigilance regulation in those patients.

1. Introduction

Patients with dementia are 55 million worldwide (World Health Organization, WHO), and about 10% are due to Parkinson's disease. Parkinson's disease dementia (PDD) is caused by intraneural inclusions of Lewy bodies (mainly formed by α-synuclein protein) in subcortical and cortical regions (Aarsland et al., 2003).

From the clinical point of view, PDD patients suffer from: (i) typical primary motor symptoms, such as akinesia, tremor, postural instability, and rigidity; (ii) cognitive deficits, such as visuospatial, verbal, and executive impairments (Levy et al., 2000; Aarsland et al., 2003; Buter et al., 2008); and (iii) vigilance dysregulation, due to impairments in dopaminergic, noradrenergic, and cholinergic ascending activating systems (Bedard et al., 1998; Riekkinen et al., 1998; Bohnen and Albin, 2011; Hall et al., 2014; Szeto et al., 2021).

Several studies using the spectral quantitative analysis of eyes-closed resting-state electroencephalographic (rsEEG) rhythms recorded from the scalp have investigated the cortical electric activity related to quiet vigilance in wakefulness in PDD patients (for a recent review, see Shirahige et al., 2020). In that eyes-closed condition, posterior cortical areas typically show a prominent oscillatory electrophysiological activity around 8–12 Hz (i.e., the alpha rhythms; Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020a).

In PDD patients, rsEEG rhythms in the eyes-closed condition are characterized by (i) an abnormally high amplitude (power) of topographically widespread rsEEG rhythms at delta (< 4 Hz) and theta (4–7 Hz) frequency bands and (ii) a poor amplitude of the posterior rsEEG rhythms at alpha frequency band (Serizawa et al., 2008; Bonanni et al., 2008; Kamei et al., 2010; Pugnetti et al., 2010; Babiloni et al., 2017). Furthermore, abnormalities in the individual rsEEG delta and alpha rhythms were related to global cognitive deficits, motor deficits, and visual hallucinations in PDD patients (Babiloni et al., 2020b).

In the healthy brain, another promising neurophysiological biomarker is the amplitude (reactivity or desynchronization) reduction of the posterior rsEEG alpha rhythms in the transition from the eyes-closed to -open condition (Babiloni et al., 2020a). In the eyes-open condition, most cortical neurons oscillating at the idling alpha frequencies may receive sensory signals from thalamocortical projections and change to an oscillatory activity higher than 30 Hz with a global increase in cortical arousal and vigilance level (Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020a). Furthermore, both cortical and thalamocortical neurons may receive excitatory signals from cholinergic basal forebrain projections, thus suggesting that impaired rsEEG alpha reactivity may serve as a neurophysiological biomarker of the integrity of the ascending, activating thalamocortical and cholinergic systems in relation to vigilance level (Wan et al., 2019; Babiloni et al., 2020a).

Keeping in mind the above data and considerations, previous studies reported the following features of the rsEEG alpha reactivity to the eyes-open condition in patients with dementing disorders: (i) lower alpha reactivity in patients with dementia due to Alzheimer's disease (ADD) and patients with Lewy body dementia (DLB, N = 24) or PDD (N = 14) when compared to matched cognitively-unimpaired old (Healthy) seniors (Schumacher et al., 2020); and (ii) lower alpha reactivity in PDD and DLB patients than ADD patients (Schumacher et al., 2020).

Recently, the present Eurasian Consortium (PDWAVES, www.pdwaves.eu) performed a study of the rsEEG alpha reactivity to the resting-state eyes-open condition in ADD and DLB patients introducing three methodological improvements (Babiloni et al., 2022): (i) the spatial analysis of the alpha reactivity was enhanced by the estimation of rsEEG cortical sources (eLORETA; Pascual-Marqui, 2007); (ii) the frequency analysis of the alpha rhythms was performed on an individual basis using the transition frequency (TF) from theta to alpha bands and the individual alpha frequency peak (IAF) (Klimesch et al., 1998); and (iii) "true" alpha rhythms were defined by two core features such as a clear posterior rsEEG spectral power peak in an extended alpha range during the eyes-closed condition and an evident alpha reactivity from the eyes-closed to -open condition. Results showed that the percentage of participants with substantial (greater than −10%) reduction (reactivity) in the posterior alpha source activities from the eyes-closed to -open condition was lower in the ADD (77%) and DLB (64%) patients than in the Healthy (93%) seniors (Babiloni et al., 2022). In the alpha-reactive participants, the reactivity to the eyes opening in the posterior rsEEG alpha source activities was lower (i) in the ADD and DLB groups than in the healthy control group and (ii) in the DLB than in the ADD group (Babiloni et al., 2022).

In the present retrospective and explorative study, we used the general rsEEG methodology of our previous reference study (Babiloni et al., 2022) to test the hypothesis that the reactivity of posterior rsEEG alpha rhythms during the transition from eyes-closed to -open condition may be lower in PDD patients than in ADD patients.

2. Materials and Methods

2.1. Participants

The clinical and rsEEG datasets for the present investigation were taken from the Eurasian archive of The PDWAVES Consortium (www.pdwaves.eu) and the European DLB Consortium. Specifically, those data referred to demographic-matched (i.e., the groups had the same mean values of age, gender, and sex ratio) PDD (N = 73), ADD (N = 35), and Healthy (N = 25) participants having rsEEG recordings with eyes-closed and eyes-open conditions. Table 1 summarizes the relevant demographic and clinical (i.e., Mini-Mental State Examination, MMSE, score) information about the Healthy, ADD, and PDD groups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between these groups regarding age (ANOVA), sex (Freeman-Halton test), education (ANOVA), and MMSE score (Kruskal-Wallis test). As expected,

Table 1
Mean values (± standard error of the mean, SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the groups of cognitively normal older adults (Healthy, N = 25) and patients with dementia due to Alzheimer's disease (ADD, N = 35) and Parkinson's disease (PDD, N = 73). Legend: M/F = males/females; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

Demographic and Clinical Data in Healthy, ADD, and PDD Participants

	Healthy	ADD	PDD	Statistical Analysis
N	25	35	73	
Age (mean years ± SE)	72.4 ± 1.6	73.0 ± 1.1	72.7 ± 0.7	ANOVA: n.s.
Sex (M/F; % of M)	18/7; 72%	27/8; 77%	61/12; 83%	Freeman-Halton: n.s.
Education (mean years ± SE)	9.9 ± 0.8	9.7 ± 0.5	9.4 ± 0.5	ANOVA: p = n.s.
MMSE (mean score ± SE)	27.7 ± 0.3	19.3 ± 0.8	18.9 ± 0.5	Kruskal-Wallis test:H = 56.6, p = 0.00001; Healthy > ADD, PDD

statistically significant differences were found between the Healthy and the other two groups for the MMSE score ($H = 56.6$, $p < 0.00001$), showing a higher score in the Healthy than the ADD and PDD groups (post-hoc test = $p < 0.00001$). On the contrary, no statistically significant differences in age, sex, and education were found between the groups ($p > 0.05$).

The local institutional ethical committees approved the study. All experiments were performed with each participant or caregiver's informed and overt consent, per the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local institutional review boards.

It should be remarked that all datasets of the alpha source reactivity to eye-opening used in the present 73 PDD patients were unpublished. In contrast, about 50% of datasets of the alpha source reactivity to eyes opening of the present 25 Healthy and 35 ADD control persons were previously used in the mentioned reference study by Babiloni et al. (2022). See Supplementary materials, *Diagnostic criteria,* for a detailed description of the clinical diagnostic criteria and cognitive screening in line with that study by Babiloni et al. (2022).

2.2. The rsEEG recordings

Electrophysiological data were recorded by professional digital EEG systems licensed for clinical applications.

All rsEEG recordings (0.3–70 Hz bandpass) were performed in the late morning. The rsEEG recordings were performed in all participants using at least 30 scalp exploring electrodes placed according to the 10–10 system. These electrodes were denoted as "selected electrodes." Their location is illustrated in Fig. 1.

Horizontal electrooculographic (EOG) potentials (0.3–70 Hz bandpass) were also recorded to control eye movements and blinking.

The rsEEG recording lasted 3–5 min in the condition of eyes closed, followed by 3–5 min in the condition of eyes open. Only the first minute of rsEEG data in the condition of eyes open (when the rsEEG alpha reactivity is supposed to be well-represented) was considered in the further analyses. Participants fixed a black cross on a white wall when they opened their eyes.

It should be remarked that the datasets of the eyes opening used in the present 73 PDD patients were unpublished. In contrast, about 50% of datasets of the eyes opening relative to the present 25 Healthy and 35 ADD control persons were re-used from the previous reference investigation by Babiloni et al. (2022).

2.3. Preliminary rsEEG data analysis

The rsEEG data were centrally analyzed by experts blinded to the participants' diagnosis by the Sapienza University of Rome unit. The recorded rsEEG data were exported as a European data format (.edf) or EEGLAB set (.set) files and then processed offline using the EEGLAB toolbox (Delorme A and Makeig S, 2004; version eeglab14_1_2b) running in the MATLAB software (Mathworks, Natick, MA, USA; version: R2014b). The rsEEG data were divided into epochs lasting 2 s (i.e., 5 min = 150 rsEEG epochs of 2 s for each experimental condition) and analyzed offline.

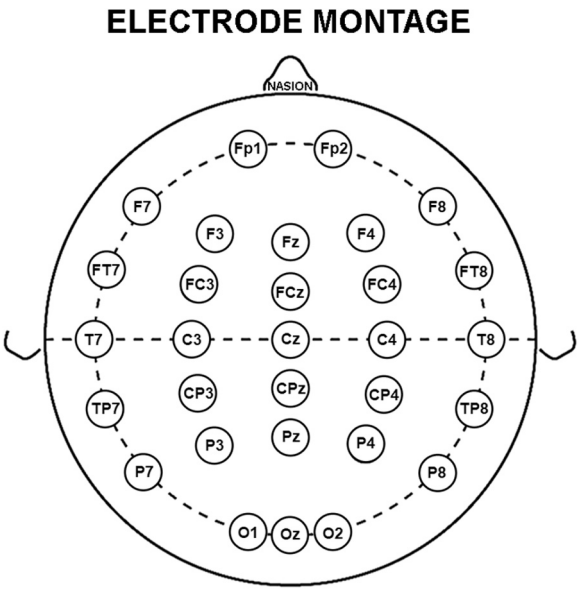

Fig. 1. Electroencephalographic (EEG) electrode montage. The electrode montage included 30 scalp monopolar sensors placed following the 10–10 System (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz and O2). This montage was used to record the resting-state EEG (rsEEG) activity during the eyes-closed condition, followed by the eyes-open condition.

Afterward, they received a 3-step procedure aimed at detecting and removing (i) recording channels (electrodes) showing prolonged artifactual rsEEG activity due to bad electric contacts or other reasons; (ii) rsEEG epochs with artifacts at recording channels characterized by general good signals; and (iii) intrinsic components of the rsEEG epochs with artifacts (see Supplementary Materials, *Preliminary rsEEG data analysis* for more details).

As a result of the above procedures, the artifact-free epochs showed a similar proportion (greater than 75%) of the total amount of rsEEG activity recorded in all groups of participants (i.e., Healthy, ADD, PDD).

2.4. Spectral analysis of the rsEEG epochs

A standard digital FFT-based analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of artifact-free rsEEG epochs at all 30 scalp electrodes (0.5 Hz of frequency resolution). From those spectral solutions, the rsEEG frequency bands of interest were individually identified based on the following frequency landmarks: transition frequency (TF) and background frequency (BGF) observed in the eyes-closed condition. In the ***eyes-closed*** rsEEG power density spectrum, the TF was defined as the minimum rsEEG power density between 3 and 8 Hz, while the BGF peak was defined as the maximum power density peak between 6 and 14 Hz. The TF and BGF were computed for each participant involved in the study. Based on the TF and BGF, we estimated the individual delta, theta, and BGF bands as follows: delta from TF − 4 Hz to TF − 2 Hz, theta from TF − 2 Hz to TF, low BGF (BGF 1 and BGF 2) from TF to BGF peak, and high-frequency BGF (or BGF 3) from BGF to BGF + 2 Hz. Specifically, the individual BGF 1 and BGF 2 bands were computed as follows: BGF 1 from TF to the

frequency midpoint of the TF-BGF range and BGF 2 from that midpoint to BGF peak. The other bands were defined based on the standard fixed frequency ranges used in the reference rsEEG studies of our Consortium (Babiloni et al., 2017a, 2017b, 2019, 2020b): beta 1 from 14 to 20 Hz, beta 2 from 20 to 30 Hz, and gamma from 30 to 40 Hz.

As mentioned in the Introduction, the BGF was considered alpha only if there was a substantial reactivity (%) of the rsEEG source activity from the eyes-closed to -open condition in posterior (parietal, temporal, and occipital) cortical regions. See the next methodological sections for more details.

2.5. Estimation of rsEEG source activation

The rsEEG source activity was estimated within the cortical source compartment of a mathematical model of an MRI-based head volume conductor (i.e., MNI-152), using an improved version of LORETA freeware (Pascual-Marqui et al., 2002) called exact LORETA (eLORETA; Pascual-Marqui, 2007). For each participant, condition (i.e., eyes-closed and eyes-open), and frequency band of interest (i.e., from delta to gamma), the estimated rsEEG source activities were the eLORETA current density solutions obtained at the frontal, central, parietal, occipital, and temporal macroregions of interest (ROIs) of the cortical source model (see Supplementary Materials, *Estimation of rsEEG source activation* for more details).

2.6. The computation of the rsEEG background frequency (BGF) reactivity

To analyze the rsEEG BGF source reactivity from the eyes-closed to -open condition, we considered the eLORETA source solutions estimated in a "posterior" ROI formed by the central, parietal, and occipital ROIs. Specifically, the rsEEG BGF reactivity was measured at the BGF 2 frequency band, which showed the maximum rsEEG source activities in the Healthy participants during the eyes-closed condition. To avoid habituation effects in the eyes-open condition, that reactivity was computed based on the eLORETA solutions estimated during the first minute of that condition, when the rsEEG BGF reactivity is generally maximum.

The rsEEG BGF reactivity from the eyes-closed to -open condition was computed by the following formula:

$$\text{Reactivity}(\%) = \frac{\text{eyes open} - \text{eyes } \textit{closed}}{\text{eyes } \textit{closed}} * 100$$

According to this definition, the percent negative values (i.e., lower BGF source activities during the eyes-open than the eyes-closed condition) indexed a ***reduction*** (reactivity) in the rsEEG BGF source activities from the eyes-closed to -open condition (Babiloni et al., 2010; Del Percio et al., 2011). This reduction is interpreted as increased cortical arousal and vigilance levels (Babiloni et al., 2020a). On the contrary, the percent positive values (i.e., greater rsEEG BGF source activities during the eyes-open than the eyes-closed condition) indexed an ***increase*** in the source rsEEG BGF activities from the eyes-closed to -open condition. This increase is interpreted as diminished cortical arousal and vigilance levels (Babiloni et al., 2020a).

Fig. 2 (top) plots the individual values of the reactivity (%) of the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity from the eyes-open (1 min) to the eyes-closed (5 min) condition for all Healthy (N = 25), ADD (N = 35) and PDD (N = 73) participants. Interestingly, about 40% of the PDD patients showed increased source BGF activities from the eyes-closed to the eyes-open condition.

Fig. 2 (bottom) illustrates the percentage of BGF (alpha)-reactive Healthy, ADD, and PDD subjects for different values of the reactivity threshold of the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity. The percentage of BGF-reactive Healthy subjects did not change when the reactivity threshold changed between 0% and − 25%; that percentage remained at 88.0% (22 BGF-reactive Healthy participants). On the contrary, the percentage of BGF-reactive ADD and PDD

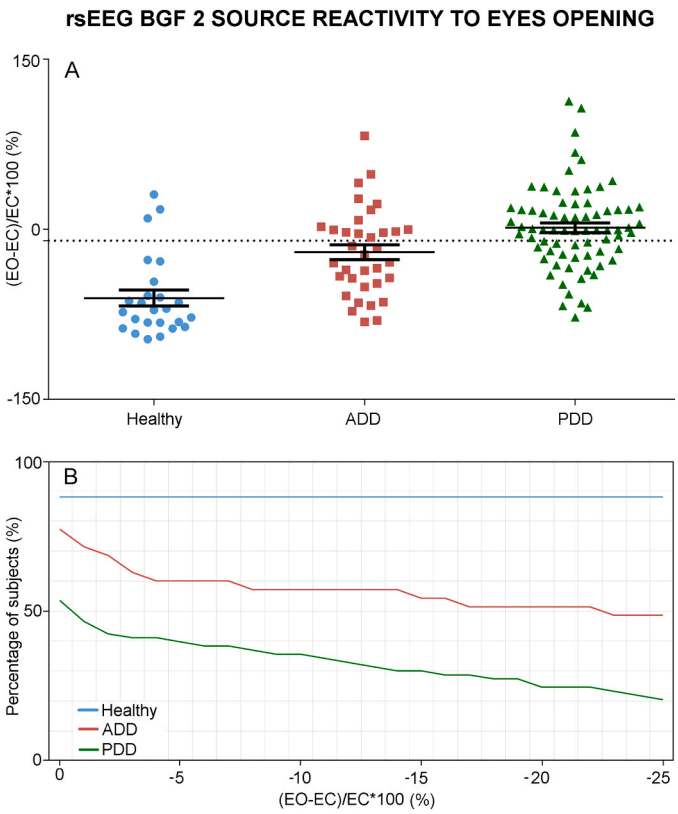

Fig. 2. (a) (Top): Individual and mean (± standard error of the mean, SE) values of the reactivity (%) of the posterior (central, parietal, and occipital) rsEEG (eLORETA) background frequency 2 (BGF 2) source activity from the eyes-closed (5 min) to -open (1 min) condition in cognitively unimpaired old adults (Healthy, N = 25) and in patients with dementia due to Alzheimer's disease (ADD, N = 35) and Parkinson's disease (PDD, N = 73). (b) (Bottom): Cumulative frequency (%) of Healthy, ADD, and PDD participants showing the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 (alpha 2) source reactivity as a function of the reactivity threshold from 0% to − 25%. (c) If the posterior rsEEG BGF source reactivity from the eyes-open to -closed condition was reduced under a given reactivity threshold (e.g., −10%), it was called "alpha." The BGF 2 (alpha 2) was defined as BGF to BGF – 2 Hz, while BGF 3 (alpha 3) was defined as BGF to BGF + 2 Hz (see Methods for more details). (d) That reactivity was computed with the following formula: the posterior (parietal, temporal, and occipital) rsEEG BGF 2 source activity during the eyes-open (EO) condition minus that source activity during the eyes-closed (EC) condition ratio of the rsEEG BGF 2 source activity during the eyes-closed (EC) condition X 100 (%). (e) Notably, the BGF was defined at a frequency ranging from 6 to 14 Hz that showed the maximum posterior (parietal, temporal, and occipital) rsEEG source activity during the resting-state eyes closed condition.

patients decreased when the reactivity threshold changed between 0% and − 25%. Notably, the percentage of BGF-reactive subjects was lower in (i) the PDD and ADD groups than the Healthy group and (ii) the PDD group than the ADD group. Specifically, the percentage of BGF-reactive ADD patients decreased from 77.1% (27 BGF-reactive ADD patients) to 48.6% (17 BGF-reactive ADD patients). The percentage of BGF-reactive PDD patients decreased from 53.4% (39 BGF-reactive PDD patients) to 20.5% (15 BGF-reactive PDD patients).

In line with a previous reference study (Babiloni et al., 2022), we used an arbitrary threshold of BGF (alpha) 2 source reactivity set at − 10%. Based on this threshold value, the BGF 2 source reactivity was seen in 22 out of 25 (88%) Healthy seniors, 20 out of 35 ADD (57%) patients, and 26 out of 73 (35%) PDD patients. The BGF 2 was considered "alpha 2" only if there was a reduction ("reactivity") of the rsEEG source activity under that reactivity threshold of − 10%. The following

analyses denoted the persons showing the rsEEG BGF 2 source reactivity as "alpha-reactive" participants. Fisher tests ($p < 0.05$) showed a statistically significant reduction of the percentage of "alpha-reactive" participants in (i) the PDD ($p < 0.00001$) and ADD ($p < 0.01$) groups than the Healthy group and (ii) the PDD group than the ADD group ($p < 0.05$).

Table 2 summarizes the most relevant demographic (i.e., age, sex, and education) and clinical (i.e., MMSE score) features of the subgroups of the alpha-reactive Healthy, alpha-reactive ADD, alpha-reactive PDD, alpha-nonreactive ADD, and alpha-nonreactive PDD participants. Furthermore, Table 3 reports the results of the presence or the absence of statistically significant differences ($p < 0.05$) among the five groups for the age (ANOVA), sex (Freeman-Halton test), education (analysis of variance, ANOVA), and MMSE score (Kruskal-Wallis test). As expected, a statistically significant difference was found for the MMSE score ($H = 56.6$, $p < 0.00001$), showing a higher score in the alpha-reactive Healthy group than in the demented groups (post-hoc test = $p < 0.0001$). On the contrary, no statistically significant differences were found in age, sex, and education among all demented groups ($p > 0.05$).

2.7. Statistical analysis of background reactivity in Healthy, ADD, and PDD groups

Two statistical sessions were performed to evaluate the clinical relevance of the background reactivity in Healthy, ADD, and PDD participants.

As a first statistical analysis at the individual level, the Spearman test ($p < 0.05$) evaluated the correlation between the MMSE score, as an index of the global cognitive status, and the reactivity (%) of the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity from the eyes-closed to -open condition, as an index of background reactivity. That correlation analysis was performed considering all Healthy, ADD, and PDD individuals as a whole group for 2 reasons. On the one hand, the hypothesis was that background reactivity may correlate with the global cognitive status of seniors, including cases with both normal and impaired cognitive functions. On the other hand, the correlation study would have had a low statistical sensitivity if performed only in the separate groups, owing to the limited scatter of global composite cognitive scores within a given group. This statistical analysis was performed by the STATISTICA software, version 10.0 (StatSoft Inc., www.statsoft.com).

As a second statistical analysis at the individual level, the reactivity (%) of the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity from the eyes-closed to -open condition as an index of background reactivity was used as a discriminant variable for the classification of the Healthy, ADD, and PDD participants. These classifications were performed by GraphPad Prism software (GraphPad Software, Inc., California, USA) using its implementation of ROC curves (DeLong et al., 1988). The following indexes measured the results of the binary classifications: sensitivity, specificity, accuracy, and AUROC curve.

Table 3
Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the groups of Healthy participants ($N = 25$), PPD patients ($N = 65$), and patients with dementia due to Lewy Body disease (DLB, $N = 30$). Legend: M/F = males/females; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

Demographic and Clinical Data in Healthy, ADD, and DLB Participants

	Healthy	PDD	DLB	Statistical Analysis
N	25	65	30	
Age (mean years ± SE)	72.4 ± 1.6	72.6 ± 0.8	72.7 ± 0.7	ANOVA: n.s.
Sex (M/F; % of M)	18/7; 72%	54/11; 83%	22/8; 73%	Freeman-Halton: n.s.
Education (mean years ± SE)	9.9 ± 0.8	9.8 ± 0.5	8.9 ± 0.5	ANOVA: n.s.
MMSE (mean score ± SE)	27.7 ± 0.3	19.5 ± 0.6	19.5 ± 0.6	Kruskal-Wallis test:H = 38.5, p = 0.00001; Healthy > DLB, PDD

2.8. Statistical analysis of rsEEG source activities in alpha-reactive Healthy, ADD, and PDD groups

Two main statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com). ANOVAs were computed using the eLORETA current density (rsEEG source activation) solutions as the dependent variables. Duncan test was used for post-hoc comparisons ($p < 0.01$). The results of the statistical analyses were controlled by the Grubbs test ($p < 0.01$) for the presence of outliers.

The first statistical session tested the control hypothesis that the rsEEG alpha source activities may be reduced from the eyes-closed to -open condition within each alpha-reactive group of interest (i.e., alpha-reactive Healthy, alpha-reactive ADD group, alpha-reactive PDD). To address this aim, an ANOVA was computed using the rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). The ANOVA used the following factors: Group (alpha-reactive Healthy, alpha-reactive ADD, and alpha-reactive PDD), Condition (eyes-open and eyes-closed), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (central, parietal, and occipital). The clinical unit was used as a covariate.

The second statistical session tested the working hypothesis that the reactivity of posterior rsEEG alpha rhythms during the transition from eyes-closed to -open condition might be lower in the alpha-reactive PDD patients than in the alpha-reactive ADD patients. To this aim, an ANOVA was computed using the reactivity of posterior (i.e., central, parietal, and occipital) rsEEG (eLORETA) alpha source activity from the eyes-closed to -open condition as a dependent variable ($p < 0.05$). The ANOVA factors were Group (alpha-reactive Healthy, alpha-reactive ADD, and alpha-reactive PDD), Band (alpha 2 and alpha 3), and ROI (central, parietal, and occipital). The clinical unit was used as a covariate.

Table 2
Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of the alpha-reactive Healthy ($N = 22$), alpha-reactive ADD ($N = 20$), alpha-reactive PDD ($N = 26$), alpha-nonreactive ADD ($N = 15$), and alpha-nonreactive PDD ($N = 47$) participants. Legend: M/F = males/females; n.s. = not significant ($p > 0.05$); MMSE = Mini Mental State Evaluation.

Demographic and Clinical Data in the Subgroups of the Alpha-reactive and Alpha-nonreactive Participants

	Alpha-reactiveHealthy	Alpha-reactiveADD	Alpha-reactivePDD	Alpha-nonreactiveADD	Alpha-nonreactivePDD	Statistical Analysis
N	22	20	26	15	47	-
Age (mean score ± SE)	72.8 ± 1.7	73.6 ± 1.4	72.9 ± 1.3	72.3 ± 1.9	72.6 ± 0.9	ANOVA: n.s.
Sex (M/F; % of M)	15/7; 68%	16/4; 80%	22/4; 85%	11/4; 73%	39/8; 83%	Freeman-Halton: n.s.
Education (mean years ± SE)	10.1 ± 0.9	9.6 ± 0.7	9.6 ± 0.8	9.7 ± 0.8	9.3 ± 0.6	ANOVA: p = n.s.
MMSE (mean score ± SE)	27.8 ± 0.4	19.4 ± 0.9	19.0 ± 1.0	19.3 ± 1.2	18.8 ± 0.6	Kruskal- Wallis test:H = 50.6, p = 0.00001

3. Results

3.1. Correlation of background reactivity and MMSE score in Healthy, ADD, and PDD groups

Fig. 3 illustrates the scatterplot showing the statistically significant negative correlation between the MMSE score and the reactivity (%) in the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity in the alpha frequencies from the eyes-closed to -open condition ($r = -0.37$; $p < 0.0001$) in all Healthy, ADD, and PDD participants (i.e., Healthy + ADD + PDD) as a whole group. The higher the reactivity (%) in the central-parietal-occipital rsEEG (eLORETA) background 2 frequency (BGF 2) source activity, the lower the MMSE score. A high alpha reactivity from the eyes-closed to the -open condition may reflect a good global cognitive status. Similarly, the correlation analysis in the Healthy + ADD participants and in the Healthy + PDD participants showed statistically significant correlations (i.e., the Healthy + ADD participants: $r = -0.45$, $p < 0.0005$; the Healthy + ADD participants: $r = -0.50$, $p < 0.0001$). On the contrary, the correlation analysis in the Healthy, ADD, and PDD participants as three separate groups did not show statistically significant results ($p > 0.05$).

3.2. Classification among Healthy, ADD, and PDD individuals based on the background reactivity

The results of the classification analysis, using the reactivity (%) of the central-parietal-occipital rsEEG (eLORETA) BGF 2 source activity from the eyes-closed to -open condition as a discriminant variable, showed: (i) a good classification accuracy for the contrast between Healthy vs. ADD individuals (AUROC = 0.80, sensitivity = 80.0%, specificity = 76.0%, accuracy = 77.7%;); (ii) a good classification accuracy for the contrast between Healthy vs. PDD individuals (AUROC = 0.88, sensitivity = 91.8%, specificity = 80.0%, accuracy = 83.0%;); and

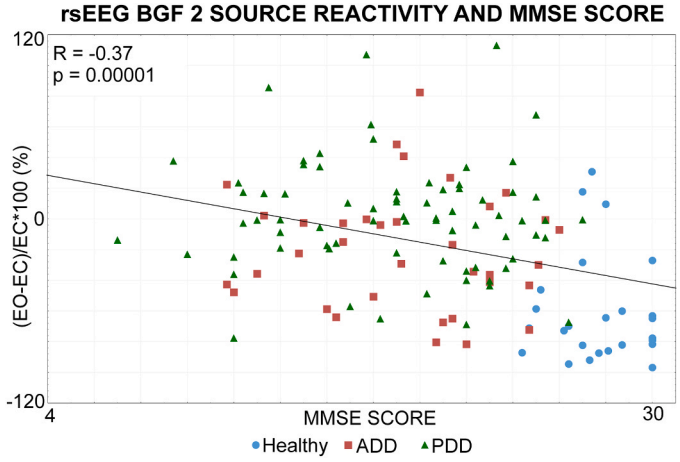

Fig. 3. Scatterplotshowing the (negative) linear Spearman test correlation between (1) thereactivity (%) of the posterior (central, parietal, and occipital) rsEEG(eLORETA) BGF 2 source activity from theeyes-closed to -open condition and(2) the Mini-Mental State Evaluation (MMSE) score. This correlation is computedin all participants of the present study (N = 133). The negative correlationderived from the variable used to measure the reduction in posterior rsEEGalpha source activity from the eyes-open to -closed condition. Negativepercentage values represent such a reduction: the greater the negativepercentage value, the greater the reduction in posterior rsEEG alpha sourceactivity during the transition from eyes-closed to -open condition. In thescatterplots, the R coefficient of the Spearman test and the relative p valuesare reported. The individual values of the (1) and (2) variables for theHealthy, ADD, and PDD persons are represented with different geometrical shapesand colors. See Figure 2 legend for more details on the formula to compute thementioned reactivity.

(iii) 3) a low classification accuracy for the contrast between ADD versus PDD individuals (AUROC < 0.70).

3.3. Distribution of rsEEG source activities in alpha-reactive Healthy, ADD, and PDD groups

In the first statistical session about the eyes-closed and eyes-open rsEEG source activities in alpha-reactive groups of Healthy (N = 22), ADD (N = 20), and PDD (N = 26) participants, the ANOVA design showed a statistical interaction effect ($F = 4.5$; $p < 0.0001$; Fig. 4) among the factors Group (alpha-reactive Healthy, alpha-reactive ADD, and alpha-reactive PDD), Condition (eyes-open, eyes-closed), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (central, parietal, and occipital). The Duncan planned post-hoc ($p < 0.01$) testing showed the following effects:

(1) In the Healthy group, the discriminant pattern eyes-closed > eyes-open was fitted by the following eLORETA solutions from rsEEG rhythms: (i) the occipital delta source activities ($p < 0.00005$); (ii) the central, parietal, and occipital theta source activities ($p < 0.0001$–0.000005); (iii) the central, parietal, and occipital alpha 1 source activities ($p < 0.0001$–0.000001); (iv) the central, parietal, and occipital alpha 2 source activities ($p < 0.000005$–0.000001); and (v) the central, parietal, and occipital alpha 3 source activities ($p < 0.000005$–0.000001). Furthermore, the discriminant pattern eyes-closed < eyes-open was fitted by the occipital rsEEG gamma source activity ($p < 0.0005$).
(2) In the ADD group, the discriminant pattern eyes-closed > eyes-open was fitted by the following eLORETA solutions from rsEEG rhythms: (i) the central, parietal, and occipital alpha 1 source activities ($p < 0.00001$–0.000001); (ii) the central, parietal, and occipital alpha 2 source activities ($p < 0.000005$–0.000001); and (iii) the central, parietal, and occipital alpha 3 source activities ($p < 0.000005$–0.000001).
(3) In the PDD group, the discriminant pattern eyes-closed > eyes-open was fitted by the following eLORETA solutions from rsEEG rhythms: (i) the parietal and occipital delta source activities ($p < 0.00005$- $p < 0.00001$); (ii) the central, parietal, and occipital theta source activities ($p < 0.0001$–0.000005); (iii) the central, parietal, and occipital alpha 1 source activities ($p < 0.0001$–0.000005); (iv) the central, parietal, and occipital alpha 2 source activities ($p < 0.000005$–0.000001); and (v) the central, parietal, and occipital alpha 3 source activities ($p < 0.000005$–0.000001).

In the second statistical session about the rsEEG alpha 2 and 3 source reactivity to eyes-opening in the alpha-reactive Healthy (N = 22), ADD (N = 20), and PDD (N = 26) participants, the ANOVA showed a statistical interaction effect ($F = 3.2$; $p < 0.01$) between the factors Group (alpha-reactive Healthy, alpha-reactive ADD, and alpha-reactive PDD) and ROI (central, parietal, and occipital). Fig. 5 depicts the variables of this statistical interaction effect. Namely, it illustrates the mean values (± SE) of the reactivity of the rsEEG (eLORETA) alpha source activities from the eyes-open to -closed (5 min) condition in the alpha-reactive Healthy, ADD, and PDD groups. In Fig. 5, the rsEEG source activities are averaged across alpha 2 and alpha 3 bands to account for the statistical interaction between Group and ROI factors. Duncan planned post-hoc ($p < 0.01$) tests showed a discriminant pattern alpha-reactive Healthy > alpha-reactive ADD > alpha-reactive PDD fitted by the parietal rsEEG alpha source activities ($p < 0.005$–0.00005). Furthermore, a discriminant pattern was alpha-reactive Healthy > alpha-reactive ADD and PDD fitted by the occipital rsEEG alpha source activities ($p < 0.005$–0.00001). Finally, there was a discriminant pattern alpha-reactive Healthy > alpha-reactive PDD fitted by the central rsEEG alpha source activities ($p < 0.005$). As the main result, the statistical

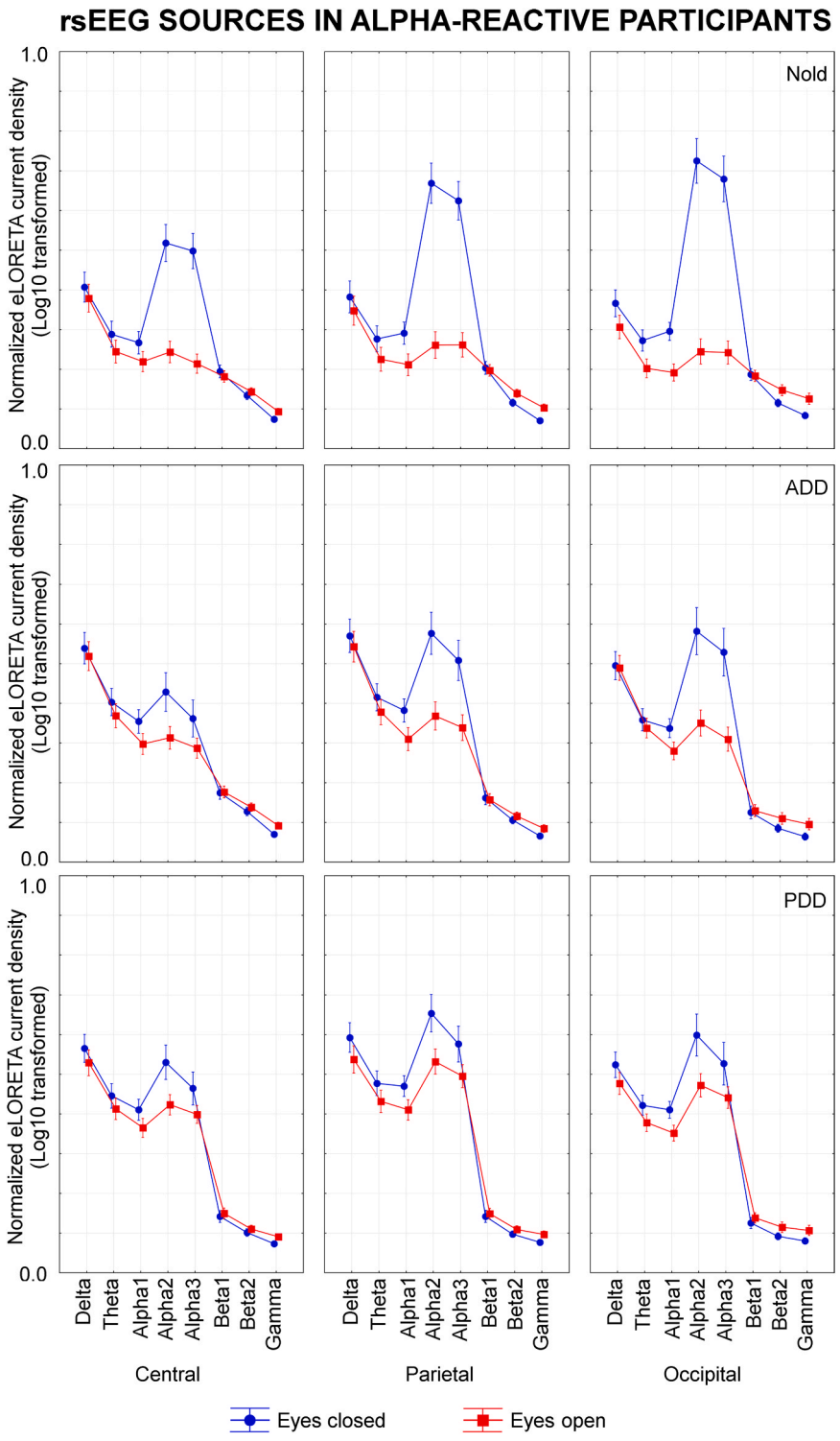

Fig. 4. Mean values (± SE) of the normalized and log-10 transformed rsEEG (eLORETA) source activities during the eyes-open and eyes-closed conditions in the alpha-reactive Healthy (N = 22), ADD (N = 19), and PDD (N = 22) persons. These values refer to the frequency bands from delta to gamma. They were statistically compared through an ANOVA design that showed a statistically significant interaction effect (F = 4.5; p < 0.0001) among the factors Group, Condition (open-eyes, EO and eyes-closed, EC), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (central, parietal, and occipital).

analysis indicated a lower parietal reactivity of the rsEEG alpha source activities in the alpha-reactive PDD group than in the alpha-reactive PDD group.

The findings mentioned above were not due to outliers from those individual regional normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.01$.

3.4. Control analyses

We performed additional control analyses to understand the core results better.

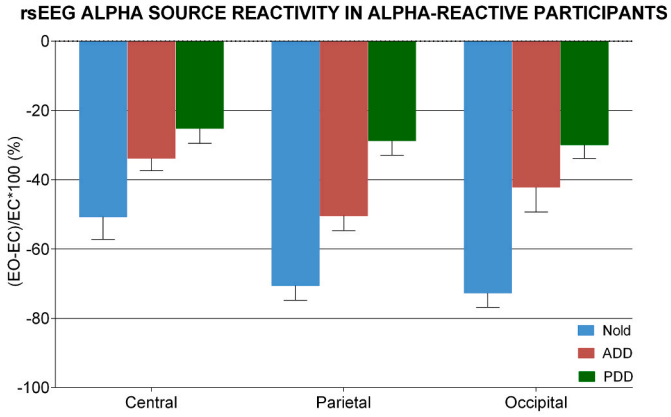

Fig. 5. Mean values (± SE) of the reactivity of thersEEG (eLORETA) source activities from the eyes-open to -closed condition inthe alpha-reactive Healthy (N = 22), ADD (N = 20) and PDD (N = 26)participants. The reactivity values were averaged from the rsEEG sourcesolutions of two core frequency bands (alpha 2 and alpha 3) and three ROIs(central, parietal, and occipital). The ANOVA of those values showed astatistical interaction effect ($F = 3.2$; $p < 0.01$) between the factors Groupand ROI, pointing to abnormally low posterior rsEEG alpha 2-3 source reactivityto the eyes-open condition in the ADD and PDD groups. This effect wassubstantially greater in the PDD group than in the ADD group.

The first control analysis was performed to evaluate whether the reactivity of posterior rsEEG alpha rhythms during the transition from eyes-closed to -open condition may be lower in PDD patients than in patients with dementia due to Lewy Body disease (DLB). To this aim, firstly, the clinical and rsEEG datasets of matched 30 DLB patients were taken from the PDWAVES and European DLB Consortia. We also considered the rsEEG data of demographic-matched PDD patients (N = 65) and Healthy seniors (N = 25), used in the main analysis (Table 3). Secondly, for each DLB participant, the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source reactivity was computed following the procedures described in the *Materials and Methods* section. Based on an arbitrary threshold of rsEEG BGF (alpha) source reactivity set at − 10%, the rsEEG BGF 2 source reactivity was seen in 22 out of 25 (88%) Healthy seniors, 23 out of 65 (37%) PDD patients, and 16 out of 30 (53%) DLB patients (Fig. 6). Fisher tests ($p < 0.05$) showed a statistically significant reduction in the percentage of "alpha-reactive" participants in the PDD than the Healthy group ($p < 0.001$). Thirdly, an ANOVA was computed using the reactivity (i.e.,

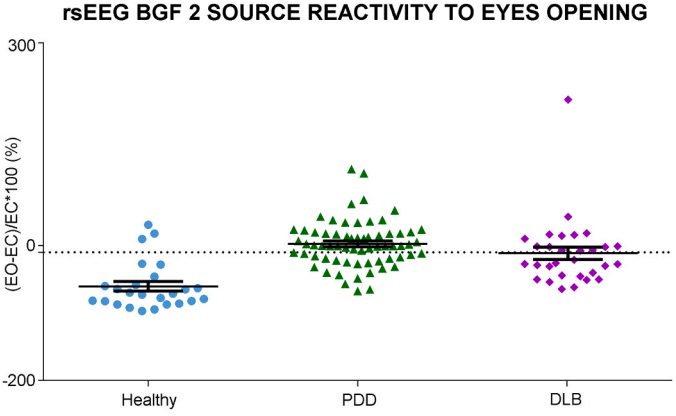

Fig. 6. Individual values of the reactivity (%) of the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source activity from the eyes-open to -closed condition in matched subgroups of Healthy (N = 25), PDD (N = 65), and DLB (N = 30) participants. See Fig. 2 legend for more details on the formula to compute the mentioned reactivity.

the reactivity of the regional normalized eLORETA solutions from rsEEG rhythms) as a dependent variable ($p < 0.05$). The ANOVA factors were Group (alpha-reactive Healthy, alpha-reactive PDD, and alpha-reactive DLB), Band (alpha 2 and alpha 3), and ROI (central, parietal, and occipital). The "clinical unit" variable was used as a covariate. The ANOVA showed a statistical interaction effect ($F = 7.4$; $p < 0.0001$; Fig. 7) between Group and ROI factors. Duncan planned post-hoc ($p < 0.01$) tests showed a discriminant pattern alpha-reactive Healthy > alpha-reactive DLB > alpha-reactive PDD fitted by the parietal rsEEG alpha source activities ($p < 0.01$–0.00005). Furthermore, there was a discriminant pattern alpha-reactive Healthy > alpha-reactive PDD and DLB fitted by the occipital rsEEG alpha source activities ($p < 0.00005$). Finally, a discriminant pattern of alpha-reactive Healthy and DLB > alpha-reactive PDD was fitted by the central rsEEG alpha source activities ($p < 0.01$–0.005). The results were confirmed even though the ANOVA did not use the mentioned covariate.

The second control analysis was performed to evaluate whether the reactivity of posterior rsEEG alpha rhythms during the transition from eyes-closed to -open condition may differ in PDD patients than in patients with PD without cognitive deficits (PDNCD). First, the clinical and rsEEG datasets of 25 PDNCD patients were taken from the Eurasian archive of the PDWAVES Consortium (www.pdwaves.eu). We also considered the rsEEG data of demographic-matched PDD patients (N = 53) and Healthy seniors (N = 20), used in the main analysis (see Table 4). Secondly, for each PDNCD participant, the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source reactivity was computed following the procedures described in the *Materials and Methods* section. Based on an arbitrary threshold of rsEEG BGF (alpha) source reactivity set at − 10%, the rsEEG BGF 2 source reactivity was seen in 18 out of 20 (90%) Healthy seniors, 19 out of 53 (36%) PDD patients, and 21 out of 25 (84%) PDNCD patients. Fisher tests ($p < 0.05$) showed a statistically significant reduction in the percentage of "alpha-reactive" participants in the PDD group than in the Healthy ($p < 0.0001$) and PDNCD ($p < 0.0005$) groups (Fig. 8). Thirdly, the Spearman test ($p < 0.05$) evaluated the correlation between the MMSE score, as an index of the global cognitive status, and the reactivity (%) of the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source activity from the eyes-closed to s-open condition, as an index of rsEEG BGF reactivity in the PDD and PDNCD individuals as a whole

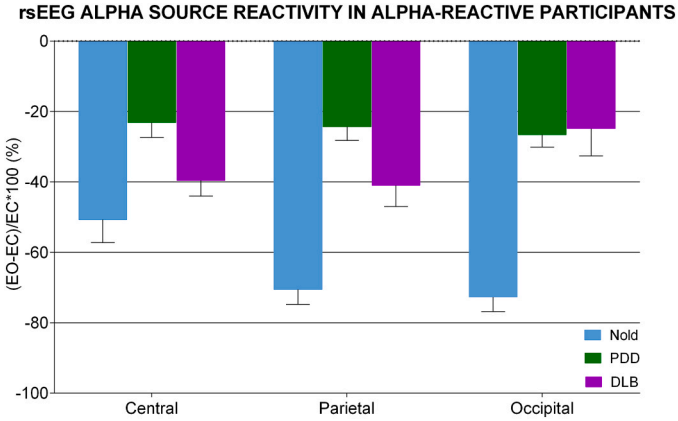

Fig. 7. Mean values (± SE) of the reactivity of thersEEG (eLORETA) source activities from the eyes-open to -closed condition in matched subgroups of alpha-reactive Healthy (N =22), PDD (N = 23), and DLB (N = 16) participants. The reactivity values wereaveraged from the rsEEG source solutions of two core frequency bands (alpha 2and alpha 3) and three ROIs (central, parietal, and occipital). The ANOVA ofthose values showed a statistically significant interaction effect ($F = 7.4$; $p< 0.0001$) between the factors Group and ROI, pointing to abnormally lowposterior rsEEG alpha 2-3 source reactivity to the eyes-open condition in thePDD and DLB groups. This effect was substantially greater in the PDD group thanin the DLB group.

Table 4
Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the groups of Healthy participants (N = 20), PPD patients (N = 53), and patients with Parkinson's disease without cognitive deficits (PDNCD, N = 25). Legend: M/F = males/females; n.s. = not significant ($p > 0.05$); MMSE = Mini Mental State Evaluation.

Demographic and Clinical Data in Healthy, PDD, and PDNCD Participants

	Healthy	PDD	PDNCD	Statistical Analysis
N	20	53	25	
Age (mean years ± SE)	70.3 ± 1.7	72.6 ± 0.8	69. ± 0.7	ANOVA: n.s.
Sex (M/F; % of M)	14/6; 70%	46/7; 87%	19/6; 84%	Freeman-Halton: n.s.
Education (mean years ± SE)	9.96 ± 0.9	9.9 ± 0.5	8.8 ± 0.9	ANOVA: n.s.
MMSE (mean score ± SE)	27.7 ± 0.4	19.4 ± 0.6	27.7 ± 0.4	Kruskal-Wallis test:H = 23.7, p = 0.0001; Healthy, PDNCD > PDD

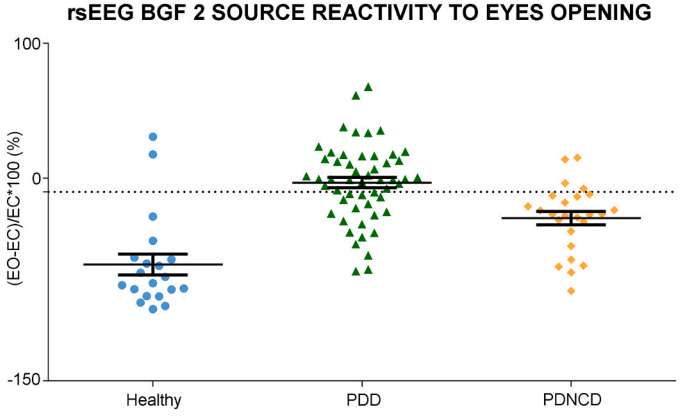

Fig. 8. Individual values of the reactivity (%) of the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source activity from the eyes-open to -closed condition in matched subgroups of Healthy (N = 20), PDD (N = 53), and PDNCD (N = 25) participants. See Fig. 2 legend for more details on the formula to compute the mentioned reactivity.

group. Fig. 9 illustrates the scatterplot showing the statistically significant negative correlation between the mentioned two markers ($r = -0.43$; $p < 0.0001$). The higher the reactivity (%) of the posterior rsEEG (eLORETA) BGF 2 source activity (expressed by negative percentage values), the lower the MMSE score. Fourthly, an ANOVA was computed using the reactivity (i.e., the reactivity of the regional normalized eLORETA solutions from rsEEG rhythms) as a dependent variable ($p < 0.05$). The ANOVA factors were Group (alpha-reactive Healthy, alpha-reactive PDD, and alpha-reactive PDNCD), Band (alpha 2 and alpha 3), and ROI (central, parietal, and occipital). The "clinical unit" variable was used as a covariate. The ANOVA showed a statistical interaction effect ($F = 3.3$; $p < 0.01$; Fig. 10) between Group and ROI factors. Duncan planned post-hoc ($p < 0.01$) tests showed a discriminant pattern of alpha-reactive Healthy > alpha-reactive PDD and PDNCD fitted by the central, parietal, and occipital rsEEG alpha source activities ($p < 0.005$–0.00005). No statistically significant difference was found between the alpha-reactive PDD and alpha-reactive PDNCD groups ($p > 0.05$). The results were confirmed even though the ANOVA did not use the mentioned covariate.

The third control analysis was performed to evaluate whether dopamine neuromodulation may affect the reactivity of posterior rsEEG source activity during the transition from eyes-closed to -open condition in PD patients. To this aim, firstly, the clinical and rsEEG datasets of 11 PD patients were taken from the Eurasian archive of the PDWAVES

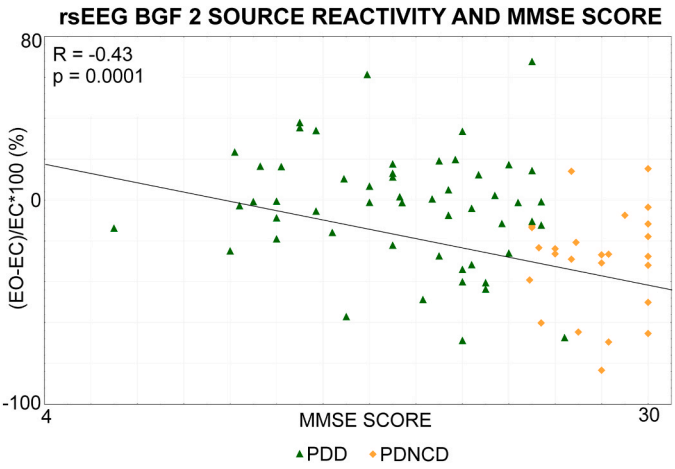

Fig. 9. Scatterplot showing the (negative) linear correlation between (1) the reactivity (%) of the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source activity from the eyes-open to -closed condition and (2) the Mini-Mental State Evaluation (MMSE) score in matched subgroups of PDNCD and PDD participants. In the scatterplots, the R coefficient of the Spearman test and the relative p values are reported. The individual values of the (1) and (2) variables for the Healthy, ADD, and PDD persons are represented with different geometrical shapes and colors. See Fig. 2 legend for more details on the formula to compute the mentioned reactivity.

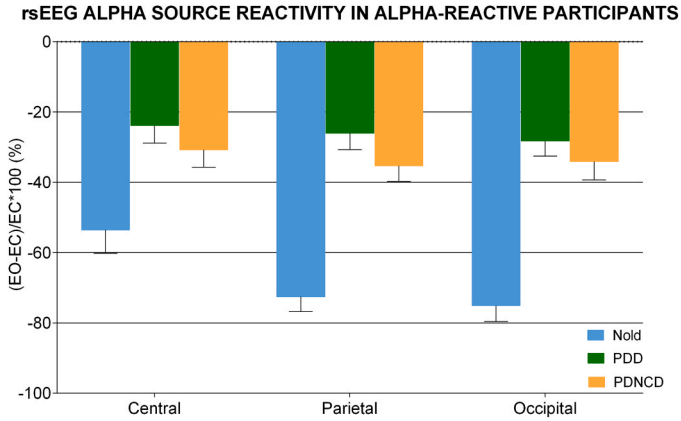

Fig. 10. The reactivity values are relative to two frequency bands (alpha 2 and alpha 3) and three ROIs (central, parietal, and occipital).
(a) Mean values (± SE) of the reactivity of the rsEEG (eLORETA) source activities from the eyes-open to -closed condition in matched subgroups of alpha-reactive Healthy (N = 18), PDD (N = 19) and PDNCD (N = 21) participants. (b) The ANOVA design showed a statistically significant interaction effect ($F = 3.3$; $p < 0.01$) between the factors Group and ROI, pointing to abnormally low posterior rsEEG alpha 2–3 source reactivity to the eyes-open condition in the PDD and PDNCD groups.

Consortium (www.pdwaves.eu). In this subgroup of PD patients under chronic therapy with levodopa, rsEEG data were recorded in the late morning before (OFF) and after (ON) about 60 min from the acute administration of 1 daily dose of levodopa. Specifically, this subgroup was formed by 1 PDD, 3 PDMCI (patients with mild cognitive impairment due to PD), and 7 PDNCD patients (3 female; mean age: 66.7 ± 2.5 SE years; mean education: 8.5 ± 1.3 SE years). Secondly, for each PD participant, the posterior (central, parietal, and occipital) rsEEG (eLORETA) BGF 2 source reactivity was computed following the procedures described in the *Materials and Methods* section. Based on an arbitrary threshold of rsEEG BGF (alpha) source reactivity set at − 10%, the rsEEG BGF 2 source reactivity was seen in 8 out of 11 (73%) PD patients in ON condition. In those alpha-reactive PD patients, the mean

value of posterior rsEEG BGF 2 source reactivity was − 34.7% (± 4.1% SE) in the ON condition and − 16.8% (± 16.1% SE) in the OFF condition. However, the T-test did not show a statistically significant difference between ON and OFF conditions ($p > 0.05$), possibly due to the small group of PD patients.

Finally, other control analyses showed that (i) the posterior rsEEG BGF source activities in the alpha frequencies were significantly ($p < 0.01$) lower in the eyes-open condition than in the eyes-closed condition within the Healthy and the ADD group but not in the PDD group (i.e., each group included alpha-reactive and non-alpha reactive participants); (ii) the posterior rsEEG BGF source reactivity during the transition from the eyes-closed to the -open condition was significantly lower ($p < 0.01$) in the PDD group than in the Healthy and the ADD groups (i.e., each group included alpha-reactive and non-alpha reactive participants); (iii) a statistically significant correlation ($p < 0.0001$) between the MMSE score and the reactivity (%) of the posterior rsEEG BGF 2 source activities from the eyes-closed to the -open condition was also observed in the subgroup of alpha-reactive persons in the Healthy, ADD, and PDD groups; (iv) the eyes-closed rsEEG source activities in the posterior regions were significantly greater in the alpha-reactive Healthy group than in the alpha-reactive ADD and PDD groups ($p < 0.001$); (v) the difference of the rsEEG alpha source reactivity in the alpha-reactive Healthy, ADD, and PDD groups was not due to the selected arbitrary thresholds for that reactivity; (vi) the rsEEG alpha source activities were not significantly reduced from the eyes-closed to -open condition within alpha-nonreactive ADD and PDD groups ($p > 0.5$). We reported more details on the methods of these control analyses and results in the Supplementary Materials, *Control analyses*.

4. Discussion

4.1. Poor rsEEG alpha reactivity to eyes opening in the PDD patients at the group level

In the present study, we tested the hypothesis that the reactivity of posterior rsEEG alpha rhythms during the transition from the eyes-closed to -open condition may be lower in PDD patients than in ADD patients. The results showed a quite low percentage (35%) of PDD patients showing substantial values of that reactivity (greater than −10%) when compared to the Healthy (88%) and ADD (57%) participants. A control analysis also showed percentages of alpha-reactive patients tendentially lower in the PDD than a control DLB group to be cross-validated in larger populations. Furthermore, these percentages were significantly lower in the PDD than in a control PD group without cognitive deficits. Considering only the alpha-reactive participants, the posterior rsEEG alpha source activities manifested lower reactivity in the PDD group than in the ADD, the control DLB, and the Healthy groups. The poor rsEEG alpha reactivity to eyes opening in the PDD patients were also observed in a control analysis including all participants (i.e., alpha-reactive and non-alpha reactive participants) in each group. The main analysis in the alpha-reactive patients provided results of interest for future intervention studies to evaluate the changes in the posterior rsEEG alpha source reactivities to the eyes-open condition during the disease progression.

These results were obtained using a group of only PDD patients, so extending previous findings showing that rsEEG alpha reactivity during the eyes-open condition was lower in a mixed group of PDD and DLB patients as compared to a Healthy group and an ADD group (Schumacher et al., 2020). The present results also extend previous findings showing less rsMEG alpha reactivity in a PDD group than in a Healthy group (Bosboom et al., 2006), emphasizing the sensitivity of a diffuse and inexpensive standard EEG technology in relation to advanced MEG systems. Notably, in those previous studies, the experimental procedure did not distinguish between participants with or without the reactivity of the rsEEG/rsMEG alpha rhythms during the eyes-open condition (Bosboom et al., 2006; Schumacher et al., 2020). Therefore, the results were not due to PDD patients showing increased background rsEEG theta or pre-alpha rhythms during the eyes-open condition. We showed many PDD patients without a reduction (reactivity) in the rsEEG alpha source activities during the eyes-open condition.

4.2. Clinical relevance of the poor rsEEG alpha reactivity in PDD individuals

Here, we showed interesting results at the individual level of the data analysis, which is important for the potential use of the present rsEEG biomarkers in the clinical management of PDD patients. There was a negative correlation ($r = - 0.37$) between the MMSE score (as a marker of global cognitive status) and the rsEEG alpha source reactivity (%) to the eyes opening in central, parietal, and occipital regions across all Healthy, ADD, and PDD participants as a whole population. The current results suggest that such alpha reactivity is clinically relevant in PDD patients and extend previous findings reporting a correlation between the MMSE score as an index of global cognitive status and biomarkers of rsEEG alpha source activity and functional connectivity in the eyes-closed condition across all Healthy, PDD, and ADD participants (Babiloni et al., 2017a, 2017b, 2018a, 2018b).

Another interesting finding of the present study was a good accuracy (i.e., 0.88 of the AUROC curve) in classifying PDD vs. Healthy individuals based on the mentioned rsEEG alpha source reactivity to the eyes open condition. This finding corroborates a bulk of previous evidence showing classification accuracies ranging from 0.95 to 0.45 in the discrimination between PPD individuals in relation to Healthy persons, based on posterior rsEEG alpha source activity and functional source connectivity estimated in the resting-state and eyes-closed condition (Lehmann et al., 2007; Snaedal et al., 2012; Babiloni et al., 2017a, 2017b, 2018a, 2018b).

4.3. A tentative pathophysiological model underpinning the poor alpha reactivity in PDD patients

At this early stage of the research in PDD patients, we do not know the pathophysiological mechanisms responsible for the dramatic poor reactivity to the eyes-open condition of posterior rsEEG alpha source activities. We can speculate about those mechanisms in the following paragraphs and hope that the proposed pathophysiological model can be tested by a future scientific program based on preclinical and clinical studies.

In physiological conditions, EEG alpha rhythms dominate the posterior cortical regions during the resting-state eyes-closed condition as a marker of cortical inhibition. They are reduced (reactivity) in amplitude during the eye-open condition (Pfurtscheller and Lopes da Silva, 1999). It can be speculated that the higher such alpha reactivity, the higher the vigilance level during wakefulness.

The amplitude of cortical rsEEG alpha rhythms may be modulated by signals (de)synchronizing the activity of cortical neural populations oscillating at alpha frequencies to produce an inhibitory (excitatory) mode (Pfurtscheller and Lopes da Silva, 1999). Among others, these signals may derive from the cortico-basal ganglia-thalamocortical and reciprocal thalamic-cortical neural circuits (Pfurtscheller and Lopes da Silva, 1999; Hughes and Crunelli, 2005; Bočková et al., 2011; Weiss et al., 2015; Sanders and Jaeger, 2016). The cortico-basal ganglia-thalamocortical neural circuit may involve (i) glutamatergic corticostriatal, subthalamic, and thalamocortical neurons; (ii) GABAergic interneurons; and (iii) dopaminergic modulatory nigrostriatal neurons. Differently, the reciprocal thalamic-cortical neural circuit may involve (i) glutamatergic thalamocortical high-threshold neurons, (ii) glutamatergic thalamocortical relay-mode neurons, (iii) GABAergic neurons of the reticular thalamic nucleus; and (iv) glutamatergic corticothalamic neurons (Hughes and Crunelli, 2005; Lörincz et al., 2008; Crunelli et al., 2015, 2018).

The cortico-basal ganglia-thalamocortical and the reciprocal

thalamic-cortical neural circuits may be mainly modulated by subcortical ascending activating neural systems. Among others, those systems are characterized by (i) noradrenergic ascending projections from locus coeruleus in the pons for alerting, (ii) dopaminergic ascending projections from midbrain nuclei for the support and reinforcement of motor actions, and (iii) cholinergic ascending projections from basal forebrain for the implementation of focused attention (Hughes and Crunelli, 2005; Lörincz et al., 2008; Crunelli et al., 2015, 2018; Li et al., 2018; Vorobyov et al., 2019; Broncel et al., 2020; Moënne-Loccoz et al., 2020; Noei et al., 2022).

The inputs from the mentioned neuromodulatory projections may induce (i) the enhancement (synchronization) in alpha rhythms, inhibiting the local information processing in cortical regions irrelevant to the ongoing event, and (ii) the block (desynchronization) of alpha rhythms associated with the enhancement (synchronization) in theta rhythms phase-coupled with the enhancement in beta and gamma rhythms, promoting the event-related local information processing, e.g., the elaboration of visual stimuli and visuomotor transformations (Pfurtscheller and Lopes da Silva; , 1999; Hughes and Crunelli, 2005; Crunelli et al., 2015; Babiloni et al., 2020a).

How does PDD-related neuropathology affect the regulation of vigilance in humans? It can be speculated that such pathology may particularly alter the dopaminergic and cholinergic neurotransmissions from the mentioned subcortical ascending activating systems to the cortico-basal ganglia-thalamocortical and the reciprocal thalamic-cortical neural circuits.

Concerning the human data on cholinergic neuromodulation, a previous MRI study in healthy young adults showed that the functional connectivity between the cholinergic basal forebrain and the occipital cortex increased from the resting-state eyes-closed to -open condition proportionally to the reactivity (i.e., desynchronization) of posterior rsEEG alpha rhythms (Wan et al., 2019). Furthermore, from MRI data, structural lesions in the white-matter connectivity between the cholinergic basal forebrain and the occipital cortex were related to reduced rsEEG alpha reactivity to the eyes-open condition in aged adults (Wan et al., 2019).

Concerning the human data on dopaminergic neuromodulation, positron emission tomography (PET) in healthy individuals showed that the pharmacological enhancement of dopaminergic transmission increased regional cerebral blood flow mainly in the anterior cingulate areas, which is a node of the default mode network maintaining the resting state condition (Kapur et al., 1994; Grasby et al., 2012). Furthermore, pharmacological enhancement also induced a widespread modulation in PD patients' cortical delta and alpha sources during the resting-state condition (Babiloni et al., 2019).

Keeping in mind the mentioned human data, the present results support the speculation that the dramatic loss of rsEEG alpha reactivity to the eyes-open condition in the PDD patients (e.g., only about 35% of the PDD patients showed a substantial alpha reactivity to the eyes-open condition) may be mainly due to the stronger impairment of the ascending dopaminergic neuromodulation in the PDD than the ADD patients. Indeed, it is well-known that the impairment of the ascending dopaminergic neuromodulation is greater in PDD than in ADD patients, while the impairment of the ascending cholinergic neuromodulation is expected to be greater in ADD than in PDD patients. This speculation is grounded on very preliminary data from a control analysis of the present study. We showed that in a small group of alpha-reactive PD patients, a clear (but statistically non-significant at $p < 0.05$) increase in the reactivity in the posterior rsEEG alpha source activities was observed in the levodopa ON over OFF condition. Future work in a larger group of PDD patients may test this speculative explanation by evaluating the rsEEG alpha reactivity to the eyes-open condition in the state ON and OFF by the levodopa administration.

4.4. Methodological remarks

In this retrospective and exploratory study, clinical and rsEEG datasets were derived from clinical units that did not follow a preliminary phase of harmonization of the standard operating procedures for the data collection in a prospective clinical trial. Furthermore, we could find only a relatively small number of PDD datasets showing rsEEG alpha reactivity from the archive of the present Consortium (www.pdwaves.eu), so we had to use a liberal statistical post-hoc test threshold of $p < 0.01$. Therefore, a future multicentric study should cross-validate the present findings with a larger group of PDD patients, a perfectly balanced number of cases and controls in each clinical unit, and a more conservative statistical threshold to mitigate the risk of false-positive discoveries with multiple comparisons. Furthermore, such a future study should cross-validate the present results by systematically measuring and comparing AD-LB neuropathology from CSF and PET in relation to the present rsEEG variables, cognitive status, and neuropsychiatric profiles. Indeed, previous autopsy studies showed that ADD and DLB overlap most frequently (Dugger et al., 2014; Matej et al., 2019; Constant et al., 2022; Gu et al., 2022). A reliable method to correctly identify a patient's neuropathology antemortem would be useful because AD and DLB often have overlapping neuropsychiatric profiles.

The present study used the 10–10 montage system with 30 scalp electrodes to perform the rsEEG recordings. Noteworthy, it is not ideal for optimal spatial sampling of rsEEG activity and source analysis at high spatial resolution (Liu et al., 2018; Marino et al., 2016). Instead, an optimal rsEEG recording for that analysis may use 64–256 scalp electrodes. However, the 10–10 system with 30 scalp electrodes may be acceptable for exploratory retrospective rsEEG studies in PDD patients using source estimation techniques at low spatial resolution (Babiloni et al., 2020c). In this line, the present rsEEG spatial sampling was used to estimate sources of rsEEG rhythms in large cortical regions of interest (i.e., cortical lobes) rather than for fine source localization. Furthermore, we used the eLORETA source estimation as it is especially suitable to model spatially widespread cortical source activations due to its smoothing regulation procedures (Halder et al., 2019; Mahjoory et al., 2017; Pascual-Marqui, 2007). Overall, eLORETA source estimation of rsEEG rhythms recorded from 30 scalp electrodes can provide informative preliminary results motivating significant investments to develop subsequent cross-validation prospective studies using high-resolution EEG techniques (i.e., 64–256 sensors).

Finally, the experimental design involved only one block of eyes-closed and eyes-open conditions. Future studies will have to address the stability and reproducibility of data in repeated blocks of eyes-closed and eyes-open conditions.

5. Conclusions

Here, we hypothesized that the reactivity of posterior rsEEG alpha rhythms during the vigilance transition from eyes-closed to -open condition may be lower in PDD patients than in ADD patients. Results showed substantial reactivity (greater than −10%) in 88% of the Healthy seniors, 57% of the ADD patients, and only 35% of the PDD patients. The alpha-reactive participants had lower reactivity in the parietal rsEEG alpha source activities in the PDD group than in the Healthy and the ADD groups.

These results suggest that PDD patients may be characterized by very poor reactivity in the posterior cortical mechanisms desynchronizing rsEEG alpha rhythms in relation to increased vigilance levels as an interesting neurophysiological biomarker. This biomarker may be used as a primary endpoint for interventions with drugs or brain electromagnetic stimulations to improve vigilance regulation and quality of life in PDD patients, allowing them to follow TV programs and interactions in their social environment.

CRediT authorship contribution statement

Claudio Babiloni: Data curation,Formal analysis,Methodology, Project administration,Supervision,Validation,Writing – original draft, Writing – review & editing.**Giuseppe Noce:** Formal analysis,Validation, Data curation,Investigation,Writing - original draft,Writing - review & editing.**Federico Tucci:** Formal analysis,Validation,Writing – original draft,Writing – review & editing,Data curation.**Dharmendra Jakhar:** Formal analysis,Validation,Writing – original draft,Writing – review & editing,Data curation.**Raffaele Ferri:** Data curation,Investigation,Project administration.**Simonetta Panerai:** Data curation,Investigation, Project administration.**Valentina Catania:** Data curation,Investigation, Project administration.**Andrea Soricelli:** Data curation,Investigation, Project administration.**Marco Salvatore:** Data curation,Investigation. **Flavio Nobili:** Data curation,Investigation,Project administration. **Dario Arnaldi:** Data curation,Investigation,Project administration. **Francesco Famà:** Data curation,Investigation,Project administration. **Carla Buttinelli:** Data curation,Investigation,Project administration. **Franco Giubilei:** Data curation,Investigation,Project administration. **Marco Onofrj:** Data curation,Investigation,Project administration. **Fabrizio Stocchi:** Data curation,Investigation,Project administration. **Laura Vacca:** Data curation,Investigation,Project administration.**Fabiana Radicati:** Data curation,Investigation,Project administration.**Peter Fuhr:** Data curation,Investigation,Project administration.**Ute Gschwandtner:** Data curation,Investigation,Project administration. **Gerhard Ransmayr:** Data curation,Investigation,Project administration.**Lucilla Parnetti:** Data curation,Investigation,Project administration.**Moira Marizzoni:** Data curation,Investigation,Project administration.**Fabrizia D'Antonio:** Data curation,Investigation,Project administration.**Giuseppe Bruno:** Data curation,Investigation,Project administration.**Carlo De Lena:** Data curation,Investigation,Project administration.**Bahar Güntekin:** Data curation,Investigation,Project administration.**Ebru Yıldırım:** Data curation,Investigation,Project administration.**Duygu Hünerli Gündüz:** Data curation,Investigation, Project administration.**John Paul Taylor:** Data curation,Investigation, Project administration.**Julia Schumacher:** Data curation,Investigation, Project administration.**Ian McKeith:** Data curation,Investigation,Project administration.**Angelo Antonini:** Data curation,Investigation,Project administration.**Florinda Ferreri:** Data curation,Investigation, Project administration.**Laura Bonanni:** Data curation,Investigation, Project administration.**Maria Francesca De Pandis:** Data curation, Investigation,Project administration.**Claudio Del Percio:** Conceptualization,Data curation,Formal analysis,Investigation,Methodology,Project administration,Supervision,Validation,Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None of the authors has potential conflicts of interest to be disclosed.

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Verification

1. (a) No Author has conflicts of interest, including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) their work, or financial disclosures in the development of the present pre-competitive basic neurophysiological research, which was based on EEG recordings in demented patients and normal subjects.

1. (b) None of author's institution has contracts relating to this research through which it or any other organization may stand to gain financially now or in the future.

1. (c) Authors state that there are not other agreements of authors or their institutions that could be seen as involving a financial interest in this work.

2. The present study was developed based on the data of the informal European Consortia PDWAVES and E-DLB. The members and institutional affiliations of the Consortium are reported in the cover page of this manuscript.

3. Authors state that the data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

4. Local institutional Ethical Committees approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

5. All the authors reviewed the contents of the manuscript being submitted, approved of its contents and validated the accuracy of the data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.11.010.

References

Aarsland, D., Litvan, I., Salmon, D., Galasko, D., Wentzel-Larsen, T., Larsen, J.P., 2003. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J. Neurol. Neurosurg. Psychiat. 74 (9), 1215–1220. https://doi.org/10.1136/jnnp.74.9.1215.

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Cordone, S., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M.T., Nobili, F., Arnaldi, D., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofrj, M., Stocchi, F., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Caravias, G., Garn, H., Sorpresi, F., Pievani, M., Frisoni, G.B., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Başar, E., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Franciotti, R., De Pandis, M.F., Bonanni, L., 2017. Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study. Neurobiol. Aging 55, 143–158. https://doi.org/10.1016/j.neurobiolaging.2017.03.030.

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Cordone, S., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M.T., Nobili, F., Arnaldi, D., Famà, F., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofrj, M., Stocchi, F., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Caravias, G., Garn, H., Sorpresi, F., Pievani, M., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Başar, E., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Franciotti, R., Frisoni, G.B., Bonanni, L., De Pandis, M.F., 2017b. Abnormalities of Cortical Neural Synchronization Mechanisms in Subjects with Mild Cognitive Impairment due to Alzheimer's and Parkinson's Diseases: An EEG Study. J. Alzheimers Dis. 59 (1), 339–358. https://doi.org/10.3233/JAD-160883.

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Lopez, S., Soricelli, A., Ferri, R., Nobili, F., Arnaldi, D., Famà, F., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofrj, M.,

Stocchi, F., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Garn, H., Fraioli, L., Pievani, M., Frisoni, G.B., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Başar, E., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Franciotti, R., Taylor, J.P., Vacca, L., De Pandis, M.F., Bonanni, L., 2018a. Abnormalities of resting-state functional cortical connectivity in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study (May). Neurobiol. Aging 65, 18–40. https://doi.org/10.1016/j.neurobiolaging.2017.12.023.

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M.T., Catania, V., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Bonanni, L., Franciotti, R., Onofrj, M., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Garn, H., Fraioli, L., Pievani, M., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Başar, E., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Taylor, J.P., De Pandis, M.F., Vacca, L., Frisoni, G.B., Stocchi, F., 2018b. Functional cortical source connectivity of resting state electroencephalographic alpha rhythms shows similar abnormalities in patients with mild cognitive impairment due to Alzheimer's and Parkinson's diseases. Clin. Neurophysiol. 129 (4), 766–782. https://doi.org/10.1016/j.clinph.2018.01.009.

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M.T., Catania, V., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Bonanni, L., Franciotti, R., Onofrj, M., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Fraioli, L., Parnetti, L., Farotti, L., Pievani, M., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Taylor, J.P., McKeith, I., Stocchi, F., Vacca, L., Frisoni, G.B., De Pandis, M.F., 2019. Levodopa may affect cortical excitability in Parkinson's disease patients with cognitive deficits as revealed by reduced activity of cortical sources of resting state electroencephalographic rhythms. Neurobiol. Aging 73, 9–20. https://doi.org/10.1016/j.neurobiolaging.2018.08.010.

Babiloni, C., Barry, R.J., Başar, E., Blinowska, K.J., Cichocki, A., Drinkenburg, W.H.I.M., Klimesch, W., Knight, R.T., Lopes da Silva, F., Nunez, P., Oostenveld, R., Jeong, J., Pascual-Marqui, R., Valdes-Sosa, P., Hallett, M., 2020a. International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies. Clin. Neurophysiol. 131 (1), 285–307. https://doi.org/10.1016/j.clinph.2019.06.234.

Babiloni, C., Pascarelli, M.T., Lizio, R., Noce, G., Lopez, S., Rizzo, M., Ferri, R., Soricelli, A., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Salvetti, M., Cipollini, V., Bonanni, L., Franciotti, R., Onofrj, M., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Aarsland, D., Parnetti, L., Farotti, L., Marizzoni, M., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Taylor, J.P., McKeith, I., Stocchi, F., Vacca, L., Hampel, H., Frisoni, G.B., De Pandis, M.F., Del Percio, C., 2020b. Abnormal cortical neural synchronization mechanisms in quiet wakefulness are related to motor deficits, cognitive symptoms, and visual hallucinations in Parkinson's disease patients: an electroencephalographic study. Neurobiol. Aging 91, 88–111. https://doi.org/10.1016/j.neurobiolaging.2020.02.029.

Babiloni, C., Blinowska, K., Bonanni, L., Cichocki, A., De Haan, W., Del Percio, C., Dubois, B., Escudero, J., Fernández, A., Frisoni, G., Guntekin, B., Hajos, M., Hampel, H., Ifeachor, E., Kilborn, K., Kumar, S., Johnsen, K., Johannsson, M., Jeong, J., LeBeau, F., Lizio, R., Lopes da Silva, F., Maestú, F., McGeown, W.J., McKeith, I., Moretti, D.V., Nobili, F., Olichney, J., Onofrj, M., Palop, J.J., Rowan, M., Stocchi, F., Struzik, Z.M., Tanila, H., Teipel, S., Taylor, J.P., Weiergräber, M., Yener, G., Young-Pearse, T., Drinkenburg, W.H., Randall, F., 2020c. What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons. Neurobiol. Aging 85, 58–73. https://doi.org/10.1016/j.neurobiolaging.2019.09.008.

Babiloni, C., Lorenzo, I., Lizio, R., Lopez, S., Tucci, F., Ferri, R., Soricelli, A., Nobili, F., Arnaldi, D., Famà, F., Buttinelli, C., Giubilei, F., Cipollini, V., Onofrj, M., Stocchi, F., Vacca, L., Fuhr, P., Gschwandtner, U., Ransmayr, G., Aarsland, D., Parnetti, L., Marizzoni, M., D'Antonio, F., De Lena, C., Güntekin, B., Yıldırım, E., Hanoğlu, L., Yener, G., Gündüz, D.H., Taylor, J.P., Schumacher, J., McKeith, I., Frisoni, G.B., De Pandis, M.F., Bonanni, L., Percio, C.D., Noce, G., 2022. Reactivity of posterior cortical electroencephalographic alpha rhythms during eyes opening in cognitively intact older adults and patients with dementia due to Alzheimer's and Lewy body diseases. Neurobiol. Aging 115, 88–108. https://doi.org/10.1016/j.neurobiolaging.2022.04.001.

Bočková, M., Chládek, J., Jurák, P., Halámek, J., Baláž, M., Rektor, I., 2011. Involvement of the subthalamic nucleus and globus pallidus internus in attention. J. Neural Transm. (Vienna) 118 (8), 1235–1245. https://doi.org/10.1007/s00702-010-0575-4.

Bohnen, N.I., Albin, R.L., 2011. The cholinergic system and Parkinson disease. Behav. Brain Res 221 (2), 564–573. https://doi.org/10.1016/j.bbr.2009.12.048.

Bonanni, L., Thomas, A., Tiraboschi, P., Perfetti, B., Varanese, S., Onofrj, M., 2008. EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain 131 (Pt 3), 690–705. https://doi.org/10.1093/brain/awm322.

Bosboom, J.L., Stoffers, D., Stam, C.J., van Dijk, B.W., Verbunt, J., Berendse, H.W., Wolters, E.Ch, 2006. Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study. Clin. Neurophysiol. 117 (11), 2521–2531. https://doi.org/10.1016/j.clinph.2006.06.720.

Broncel, A., Bocian, R., Kłos-Wojtczak, P., Konopacki, J., 2020. Effects of locus coeruleus activation and inactivation on hippocampal formation theta rhythm in anesthetized rats. Brain Res Bull. 162, 180–190. https://doi.org/10.1016/j.brainresbull.2020.05.017.

Buter, T.C., van den Hout, A., Matthews, F.E., Larsen, J.P., Brayne, C., Aarsland, D., 2008. Dementia and survival in Parkinson disease: a 12-year population study. Neurology 70 (13), 1017–1022. https://doi.org/10.1212/01.wnl.0000306632.43729.24.

Constant, A.B., Basavaraju, R., France, J., Honig, L.S., Marder, K.S., Provenzano, F.A., 2022. Longitudinal patterns of cortical atrophy on mri in patients with alzheimer disease with and without lewy body pathology. Sep 19 Neurology 99 (17), e1843–e1852. https://doi.org/10.1212/WNL.0000000000200947.

Crunelli, V., David, F., Lőrincz, M.L., Hughes, S.W., 2015. The thalamocortical network as a single slow wave-generating unit. Curr. Opin. Neurobiol. 31, 72–80. https://doi.org/10.1016/j.conb.2014.09.001.

Crunelli, V., Lőrincz, M.L., Connelly, W.M., David, F., Hughes, S.W., Lambert, R.C., Leresche, N., Errington, A.C., 2018. Dual function of thalamic low-vigilance state oscillations: rhythm-regulation and plasticity. Nat. Rev. Neurosci. 19 (2), 107–118. https://doi.org/10.1038/nrn.2017.151.

DeLong, E.R., DeLong, D.M., Clarke-Pearson, D.L., 1988. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44 (3), 837–845.

Dugger, B.N., Adler, C.H., Shill, H.A., Caviness, J., Jacobson, S., Driver-Dunckley, E., Beach, T.G., Arizona Parkinson's Disease Consortium, 2014. Concomitant pathologies among a spectrum of parkinsonian disorders (May). Park. Relat. Disord. 20 (5), 525–529. https://doi.org/10.1016/j.parkreldis.2014.02.012.

Gu, Y., Kociolek, A., Fernandez, K.K., Cosentino, S.A., Zhu, C.W., Jin, Z., Leverenz, J.B., Stern, Y.B., 2022. Clinical trajectories at the end of life in autopsy-confirmed dementia patients with Alzheimer disease and lewy bodies pathologies. May 24 Neurology 98 (21), e2140–e2149. https://doi.org/10.1212/WNL.0000000000200259.

Hughes, S.W., Crunelli, V., 2005. Thalamic mechanisms of EEG alpha rhythms and their pathological implications. Neuroscientist 11 (4), 357–372. https://doi.org/10.1177/1073858405277450.

Kamei, S., Morita, A., Serizawa, K., Mizutani, T., Hirayanagi, K., 2010. Quantitative EEG analysis of executive dysfunction in Parkinson disease. J. Clin. Neurophysiol. 27 (3), 193–197. https://doi.org/10.1097/WNP.0b013e3181dd4fdb.

Kapur, S., Meyer, J., Wilson, A.A., Houle, S., Brown, G.M., 1994. Activation of specific cortical regions by apomorphine: an [15O]H2O PET study in humans. Neurosci. Lett. 176 (1), 21–24. https://doi.org/10.1016/0304-3940(94)90861-3.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., Schwaiger, J., 1998. Induced alpha band power changes in the human EEG and attention. Neurosci. Lett. 244 (2), 73–76. https://doi.org/10.1016/s0304-3940(98)00122-0.

Lehmann, C., Koenig, T., Jelic, V., Prichep, L., John, R.E., Wahlund, L.O., Dodge, Y., Dierks, T., 2007. Application and comparison of classification algorithms for recognition of Alzheimer's disease in electrical brain activity (EEG). J. Neurosci. Methods 161 (2), 342–350. https://doi.org/10.1016/j.jneumeth.2006.10.023.

Levy, G., Tang, M.X., Cote, L.J., Louis, E.D., Alfaro, B., Mejia, H., Stern, Y., Marder, K., 2000. Motor impairment in PD: relationship to incident dementia and age. Neurology 55 (4), 539–544. https://doi.org/10.1212/wnl.55.4.539.

Li, S., Franken, P., Vassalli, A., 2018. Bidirectional and context-dependent changes in theta and gamma oscillatory brain activity in noradrenergic cell-specific Hypocretin/Orexin receptor 1-KO mice. Sci. Rep. 8 (1), 15474 https://doi.org/10.1038/s41598-018-33069-8.

Liu, Q., Ganzetti, M., Wenderoth, N., Mantini, D., 2018. Detecting Large-scale Brain Networks Using EEG: impact of electrode density, head modeling and source localization. Front Neuroinform 12, 4. https://doi.org/10.3389/fninf.2018.00004.

Lörincz, M.L., Crunelli, V., Hughes, S.W., 2008. Cellular dynamics of cholinergically induced alpha (8–13 Hz) rhythms in sensory thalamic nuclei in vitro. J. Neurosci. 28 (3), 660–671. https://doi.org/10.1523/JNEUROSCI.4468-07.2008.

Marino, M., Liu, Q., Brem, S., Wenderoth, N., Mantini, D., 2016. Automated detection and labeling of high-density EEG electrodes from structural MR images. J. Neural Eng. 13 (5), 056003 https://doi.org/10.1088/1741-2560/13/5/056003.

Moënne-Loccoz, C., Astudillo-Valenzuela, C., Skovgård, K., Salazar-Reyes, C.A., Barrientos, S.A., García-Núñez, X.P., Cenci, M.A., Petersson, P., Fuentes-Flores, R.A., 2020. Cortico-striatal oscillations are correlated to motor activity levels in both physiological and parkinsonian conditions. Front Syst. Neurosci. 14, 56 https://doi.org/10.3389/fnsys.2020.00056.

Noei, S., Zouridis, I.S., Logothetis, N.K., Panzeri, S., Totah, N.K., 2022. Distinct ensembles in the noradrenergic locus coeruleus are associated with diverse cortical states. e2116507119 Proc. Natl. Acad. Sci. USA 119 (18). https://doi.org/10.1073/pnas.2116507119.

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. 110 (11), 1842–1857. https://doi.org/10.1016/s1388-2457(99)00141-8.

Pugnetti, L., Baglio, F., Farina, E., Alberoni, M., Calabrese, E., Gambini, A., Di Bella, E., Garegnani, M., Deleonardis, L., Nemni, R., 2010. EEG evidence of posterior cortical disconnection in PD and related dementias. Int J. Neurosci. 120 (2), 88–98. https://doi.org/10.3109/00207450903436346.

Riekkinen, M., Kejonen, K., Jäkälä, P., Soininen, H., Riekkinen, P.Jr, 1998. Reduction of noradrenaline impairs attention and dopamine depletion slows responses in Parkinson's disease. Eur. J. Neurosci. 10 (4), 1429–1435. https://doi.org/10.1046/j.1460-9568.1998.00145.x.

Sanders, T.H., Jaeger, D., 2016. Optogenetic stimulation of cortico-subthalamic projections is sufficient to ameliorate bradykinesia in 6-ohda lesioned mice. Neurobiol. Dis. 95, 225–237. https://doi.org/10.1016/j.nbd.2016.07.021. Epub 2016 Jul 21.

Schumacher, J., Thomas, A.J., Peraza, L.R., Firbank, M., Cromarty, R., Hamilton, C.A., Donaghy, P.C., O'Brien, J.T., Taylor, J.P., 2020. EEG alpha reactivity and cholinergic system integrity in Lewy body dementia and Alzheimer's disease. Alzheimers Res Ther. 12 (1), 46 https://doi.org/10.1186/s13195-020-00613-6.

Serizawa, K., Kamei, S., Morita, A., Hara, M., Mizutani, T., Yoshihashi, H., Yamaguchi, M., Takeshita, J., Hirayanagi, K., 2008. Comparison of quantitative EEGs between Parkinson disease and age-adjusted normal controls. J. Clin. Neurophysiol. 25 (6), 361–366. https://doi.org/10.1097/WNP.0b013e31818f50de.

Snaedal, J., Johannesson, G.H., Gudmundsson, T.E., Blin, N.P., Emilsdottir, A.L., Einarsson, B., Johnsen, K., 2012. Diagnostic accuracy of statistical pattern recognition of electroencephalogram registration in evaluation of cognitive impairment and dementia. Dement Geriatr. Cogn. Disord. 34 (1), 51–60. https://doi.org/10.1159/000339996.

Vorobyov, V., Bakharev, B., Medvinskaya, N., Nesterova, I., Samokhin, A., Deev, A., Tatarnikova, O., Ustyugov, A.A., Sengpiel, F., Bobkova, N., 2019. Loss of midbrain dopamine neurons and altered apomorphine EEG Effects in the 5xFAD mouse model of Alzheimer's disease. J. Alzheimers Dis. 70 (1), 241–256. https://doi.org/10.3233/JAD-181246.

Wan, L., Huang, H., Schwab, N., Tanner, J., Rajan, A., Lam, N.B., Zaborszky, L., Li, C.R., Price, C.C., Ding, M., 2019. From eyes-closed to eyes-open: Role of cholinergic projections in EC-to-EO alpha reactivity revealed by combining EEG and MRI. Hum. Brain Mapp. 40 (2), 566–577. https://doi.org/10.1002/hbm.24395.

Weiss, D., Klotz, R., Govindan, R.B., Scholten, M., Naros, G., Ramos-Murguialday, A., Bunjes, F., Meisner, C., Plewnia, C., Krüger, R., Gharabaghi, A., 2015. Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease. Brain 138 (Pt 3), 679–693. https://doi.org/10.1093/brain/awu380.