

Resting-state electroencephalographic rhythms depend on sex in patients with dementia due to Parkinson's and Lewy Body diseases: An exploratory study

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ABSTRACT

Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are more prevalent in males than females. Furthermore, they typically showed abnormally high delta (< 4 Hz) and low alpha (8–10 Hz)

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Resting-state electroencephalographic (EEG) rhythms
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Sex

rhythms from resting-state electroencephalographic (rsEEG) activity. Here, we hypothesized that those abnormalities may depend on the patient's sex.

An international database provided clinical-demographic-rsEEG datasets for cognitively unimpaired older (Healthy; $N = 49$; 24 females), PDD ($N = 39$; 13 females), and DLB ($N = 38$; 15 females) participants. Each group was stratified into matched female and male subgroups. The rsEEG rhythms were investigated across the individual rsEEG delta, theta, and alpha frequency bands based on the individual alpha frequency peak. The eLORETA freeware was used to estimate cortical rsEEG sources.

In the Healthy group, widespread rsEEG alpha source activities were greater in the females than in the males. In the PDD group, widespread rsEEG delta source activities were lower and widespread rsEEG alpha source activities were greater in the females than in the males. In the DLB group, central-parietal rsEEG delta source activities were lower, and posterior rsEEG alpha source activities were greater in the females than in the males.

These results suggest sex-dependent hormonal modulation of neuroprotective-compensatory neurophysiological mechanisms in PDD and DLB patients underlying the generation of rsEEG delta and alpha rhythms, which should be considered in the treatment of vigilance dysregulation in those patients.

1. Introduction

Patients with dementia are 55 million worldwide (World Health Organization, WHO), and about 10 %–20 % are due to Parkinson's and Lewy Body diseases.

Dementia due to Parkinson's (PDD) and Lewy Body (DLB) diseases are caused by intraneural inclusions of Lewy bodies (mainly formed by α -synuclein protein) in subcortical (mostly in PDD) and cortical (primarily in DLB) regions (Aarsland et al., 2003; Weisman and McKeith, 2007), causing axonal dysfunction, neuronal loss, and brain atrophy. DLB and PDD are characterized by the accumulation of α -synuclein in brain Lewy bodies and neurites, as well as a depletion of tegmental dopamine and loss of basal forebrain cholinergic cells (Barker and Williams-Gray, 2016; Gomperts et al., 2016; Hall et al., 2014; Hepp et al., 2016). Notably, previous studies showed that the incidence and prevalence of PDD are higher in males than in females (Savica et al., 2013a, 2013b; Irwin et al., 2017; Lemstra et al., 2017; Patel and Kompoliti, 2023; Ben-Shlomo et al., 2024; Grotewold and Albin, 2024).

Clinically, PDD and DLB are characterized by executive, attentional, and verbal cognitive dysfunctions in addition to the classical motor symptoms, including rest tremor, rigidity, or bradykinesia (Levy et al., 2000; Aarsland et al., 2003; Emre et al., 2007; Buter et al., 2008; Walker et al., 2015). In PD patients, motor symptoms typically manifest as the primary early symptoms, followed by the onset of cognitive decline (Aarsland et al., 2003). In DLB patients, cognitive deficits precede the development of the classical parkinsonian motor disorder. DLB patients are primarily characterized by visual hallucinations, marked diurnal cognitive fluctuation, and the presence of rapid eye movement sleep behavior disorder, RBD (McKeith et al., 2017), with some sex-dependent differences. For example, visual hallucinations may be more frequent and show earlier onset in DLB females than in males, whereas RBD may be more frequent and show earlier onset in men (Chiu et al., 2023).

Some of the above PDD and DLB symptoms may be due to vigilance dysfunctions in relation to altered dopaminergic, noradrenergic, and cholinergic ascending activating systems (Bohnen and Albin, 2011; Hall et al., 2014; Orlando et al., 2023; Caminiti et al., 2024; Simuni et al., 2024; Okkels et al., 2024). Remarkably, these dysfunctions are reflected by abnormalities in electroencephalographic (rsEEG) rhythms recorded from scalp electrodes during a resting-state eyes-closed condition, which is characterized by quiet wakefulness, psychophysiological relaxation, and mind wandering (Babiloni et al., 2020a). In cognitively unimpaired persons, rsEEG alpha rhythms (8–12 Hz) are prominent in the posterior scalp regions, while rsEEG rhythms at delta (< 4 Hz) and theta (4–7 Hz) rhythms typically show widespread, low amplitude (Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020a). Compared to those persons, PDD and DLB patients were characterized by abnormally ample rsEEG delta and theta rhythms in widespread regions and poor posterior rsEEG alpha rhythms (Walker et al., 2000; Kai et al., 2005; Serizawa et al., 2008; Bonanni et al., 2008; Jackson et al., 2008; Kamei et al., 2010; Pugnetti et al., 2010; Babiloni et al., 2017). The alterations in the rsEEG

delta and alpha rhythms were also associated with symptoms reflecting vigilance dysfunctions, such as visual hallucinations and RBD in PDD and DLB patients (Babiloni et al., 2020b; Pascarelli et al., 2020).

Keeping in mind the above data, an open issue is whether the alterations in the rsEEG rhythms may be sex-dependent in PDD and DLB patients. In this regard, previous studies unveiled the influence of sex on rsEEG rhythms in physiological and pathological aging. It was reported an interaction between sex and age on the posterior rsEEG theta rhythms recorded in healthy adults 20 to 70 years old (Veldhuizen et al., 1993). Furthermore, posterior rsEEG theta rhythms were higher in healthy females than in males 30 to 80 years old (Duffy et al., 1993). In contrast, rsEEG rhythms showed higher amplitude at several frequencies from delta to beta in healthy young females than in males (Wada et al., 1994). Notably, a previous rsEEG study conducted by our research group (Babiloni et al., 2022) demonstrated that the sex factor influenced rsEEG source activities estimated in cognitively unimpaired older (Healthy) participants and patients with mild cognitive impairment due to Alzheimer's disease (ADMCI). Among Healthy seniors, females exhibited greater amplitude of topographically widespread rsEEG alpha source activities compared to males (Babiloni et al., 2022). Similarly, female over male ADMCI patients showed greater posterior rsEEG alpha source activities (Babiloni et al., 2022).

In the present exploratory study, we tested the hypothesis that rsEEG delta and alpha source activities in PDD and DLB patients may depend on the sex factor. This hypothesis holds significance for both research and clinical applications, as PDD and DLB patients are typically characterized by higher prevalence in males than in females, suggesting protective/compensatory mechanisms acting based on sex. Furthermore, rsEEG rhythms may reflect vigilance dysfunctions in those patients. For example, rsEEG biomarkers may be used as an intervention endpoint for vigilance dysfunctions in clinical trials, and the sex factor may be used to stratify PDD and DLB patients. Furthermore, rsEEG biomarkers may be analyzed separately in males and females and provide input for sex-dependent neurophysiological models of those diseases, suggesting sex-specific therapeutical interventions in Precision Medicine.

2. Materials and methods

2.1. Participants

The present retrospective and exploratory study is based on pre-existing data from the PDWAVES Consortium (www.pdwaves.eu) and the European DLB Consortium (www.e-dlb.com). We selected 49 Healthy, 39 PDD, and 38 DLB participants stratified by sex in the following subgroups: Healthy-female ($N = 24$), Healthy-male ($N = 25$), PDD-female ($N = 13$), PDD-male ($N = 26$), DLB-female ($N = 15$), and DLB male ($N = 23$; see *Supplementary Materials, Participants* and for a detailed description of participants' selection).

Within each group (i.e., Healthy, PDD, and DLB), the female and

male subgroups were matched for age, education, and global cognitive status, ensuring that the groups did not significantly differ in age, education, and MMSE score ($p < 0.05$ uncorrected). Within each group with neurodegenerative disease (i.e., PDD and DLB), the female and male subgroups were also matched for the measures of visual hallucination (VH), Unified Parkinson's disease Rating Scale-III (UPDRS III), and probable REM behavioral disorder (RBD). More than 90 % of the participants are (non-Hispanic) White.

The local institutional ethical committees approved the study. All experiments were conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local institutional review boards. Informed and overt consent was obtained from each participant or caregiver prior to their participation.

2.2. Diagnostic criteria

The diagnosis of PD ($N = 39$) was based on a standard clinical assessment of tremor, rigidity, and bradykinesia (Gelb et al., 1999). As measures of severity of a motor disability, the Hoehn and Yahr stage (Hoehn and Yahr, 1967) and the Unified Parkinson's disease Rating Scale-III (UPDRS III; Fahn and Elton, 1987) for extrapyramidal symptoms were used (Unfortunately, data from the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale were not available). Furthermore, the diagnosis of PDD was given to patients with a history of dementia, preceded by a typical levodopa-responsive Parkinsonian motor syndrome for at least 12 months and unrelated to other pathologic conditions than PD.

The selected PDD patients did not suffer from severe tremors or dyskinesias. The PDD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, fourth edition (DSM-IV-TR; American Psychiatric Association). The following inclusion criteria were fulfilled: (1) diagnosis of PD as specified previously; (2) a gradual neurocognitive decline in the context of established PD reported by either the patient or a reliable informant or observed by clinicians; (3) an abnormally low score in at least one of the neuropsychological tests mentioned in the following section, as defined by performances beyond 1.5 times the SD from the mean value for age- and education-matched controls or equivalent scores for abnormality according to the manuals of the tests used; and (4) moderate to severe impairment in instrumental activities of the daily living and dependency. All PDD patients were under standard long-term chronic dopaminergic treatment, and all exams were performed under the ON state.

The diagnosis of the DLB ($N = 38$) was carried out according to the mentioned consensus guidelines (McKeith et al., 2017). The clinical features of the DLB patients were detected as follows: (1) the occurrence frequency and severity of hallucinations were evaluated using item-2 of the Neuropsychiatric Inventory (NPI; Cummings et al., 1994); (2) the severity of frontal dysfunction was assessed using the Frontal Assessment Battery (FAB; Dubois et al., 2000); (3) presence and severity of the cognitive fluctuations were determined using the Clinician Assessment of Fluctuations (Walker et al., 2000); (4) extrapyramidal signs were evaluated using the Unified Parkinson's disease Rating Scale-III (UPDRS-III; Fahn et al., 1987); and (5) presence and absence of RBD was determined based on the minimal International Classification of Sleep Disorders – Third Edition (ICSD-3) (2014).

Exclusion criteria for PDD and DLB patients included any evidence of (1) vascular dementia, diagnosed according to the National Institute of Neurological Disorders and Stroke (NINDS-AIREN) criteria (Román et al., 1993); (2) current participation in a clinical trial using disease-modifying drugs; (3) past or present diagnosis of major psychiatric disorders (i.e., depression, etc.) or neurological illness not related to cognitive deficits; (4) past or present diagnosis of epilepsy or report of seizures or epileptiform EEG activity in the past; (5) use of antiepileptics; and (6) past or present dependence on opiates and alcohol.

Moreover, in all PDD and DLB patients, the use of anti-hypertensive

drugs, diabetes drugs, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics, antagonists of *N*-methyl-D-aspartate receptors (NMDARs), acetylcholinesterase inhibitors (AChEIs), was allowed and controlled in the statistical contrasts of this study. The PDD and DLB patients using those drugs could take their medications immediately after rsEEG experiments, planned in the late morning. Therefore, they delayed the intake of their medications only for a few hours about their normal routine, ensuring their well-being.

Exclusion criteria for healthy seniors were (1) neurological or psychiatric diseases (previous or present), (2) presence of a depressive episode as detected by a Geriatric Depression Scale (15-item version) score higher than 5, (3) use of chronic psychoactive drugs, and (4) presence of significant chronic systemic illnesses such as diabetes mellitus.

In the study participants, the performance in various cognitive domains, including language, visuospatial function, executive function/attention, and memory, was assessed using local batteries of neuropsychological tests. Specifically, for the evaluation of cognitive functions, (1) language was tested by the Verbal fluency test for letters (Novelli et al., 1986) and the Verbal fluency test category (fruits, animals, or car trades; Novelli et al., 1986); (2) visuospatial functions were assessed by the Line Orientation test (Benton et al., 1978) and the Face Recognition test (Benton et al., 1983); (3) executive functions and attention were evaluated by the Trail Making Test Part A and B (Reitan, 1958), the Stroop test (Stroop, 1935), and the Confusion Assessment Method (executive function part; Inouye et al., 1990); and (4) memory was tested by the Digit Span Forward and Backward (Wechsler, 1987), Oktem Verbal Memory test (Oktem, 1992), and the Confusion Assessment Method (memory part; Inouye et al., 1990). Notably, each clinical unit administered one or more of the above-mentioned neuropsychological tests for each cognitive domain, according to local protocols.

2.3. The rsEEG recordings

The rsEEG recordings were conducted using local routine professional digital EEG systems licensed for clinical applications (We used the equipment brands as a covariate in the statistical models of the present study). All rsEEG recordings were performed in the morning (9:00–11:00 AM) to minimize potential variations due to circadian rhythms. Standard instructions for the resting-state condition emphasized staying awake, psychophysically relaxed with mind wandering, and following the experimenter's requests to keep the eyes closed and open during the rsEEG recording. The experiments checked the participant's behavioral state during the EEG recordings and annotated eventual deviations and alarms.

A common electrode montage of 30 scalp exploring electrodes, placed according to the 10–10 system, characterized the EEG data recordings in all clinical units and was used for the data analysis (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). These electrodes, referred to as “selected electrodes,” were positioned to cover the whole scalp. The reference electrode was typically placed between Fz and Cz of the 10–20 system, and the ground electrode was in the posterior midline. To minimize the influence of the different placement of the reference electrodes, all EEG data were re-referenced to the common average for the data analysis.

Electrooculographic (EOG) activity with a standard bipolar montage was also recorded to monitor and control eye movements and blinking. As minimum standards in all clinical units, electrophysiological data allowed a bandpass filtering of 0.3–70 Hz and a sampling rate of 256 Hz.

2.4. Preliminary rsEEG data analysis

The rsEEG data were centrally analyzed by experts by the Sapienza University of Rome unit, who were blinded to the participant's diagnosis. 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 and Makeig, 2004; version eeglab14.1.2b) running in the MATLAB software (Mathworks, Natick, MA, USA; version: R2014b).

During the preprocessing, 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 subjected to offline analysis. A three-step procedure was employed to detect and remove the following items: (1) recording channels (electrodes) showing prolonged artifactual rsEEG activity due to bad electric contacts or other reasons; (2) rsEEG epochs with artifacts at recording channels characterized by generally good signals; and (3) intrinsic components of the rsEEG epochs with artifacts (see *Supplementary Materials, Preliminary rsEEG data analysis* for more details).

2.5. Spectral analysis of the rsEEG epochs

Standard digital Fast Fourier Transform (FFT)-based analysis, employing the Welch technique with a Hanning windowing function and no phase shift, was used to compute the power density of the artifact-free rsEEG epochs recorded at all 30 scalp electrodes, with a frequency resolution of 0.5 Hz.

The rsEEG frequency bands of interest were individually identified based on specific frequency landmarks, namely the transition frequency (TF) and the individual alpha frequency (IAF). In the (eyes-closed) rsEEG power density spectrum, the TF was defined as the minimum rsEEG power density between 3 and 8 Hz. In comparison, the IAF peak was defined as the maximum power density peak between 6 and 14 Hz.

The TF and IAF were computed for each participant involved in the study. Based on TF and IAF, individual delta, theta, and alpha bands were estimated as follows: delta from TF -4 Hz to TF -2 Hz, theta from TF -2 Hz to TF, low alpha (alpha 1 and alpha 2) from TF to IAF, and high-frequency alpha (or alpha 3) from IAF to IAF + 2 Hz. Specifically, the individual alpha 1 and alpha 2 bands were computed as follows: alpha 1 from TF to the frequency midpoint of the TF-IAF range and alpha 2 from that midpoint to the IAF peak. The other bands were defined based on standard fixed frequency ranges used in the reference rsEEG studies of our Consortium (Babiloni et al., 2017, 2020b, 2022): beta 1 from 14 to 20 Hz and beta 2 from 20 to 30 Hz.

2.6. Estimation of rsEEG source activation

We used the official freeware tool called exact LORETA (eLORETA) to linearly estimate the cortical source activity generating scalp-recorded rsEEG rhythms (Pascual-Marqui, 2007). For each participant and frequency band of interest (i.e., from delta to beta 2), the estimated rsEEG source activities were the eLORETA current density solutions obtained at the frontal, central, parietal, occipital, temporal, and limbic macroregions of interest (ROIs) of the cortical source model (see *Supplementary Materials, Estimation of rsEEG source activation* for more details).

2.7. Main statistical analysis of rsEEG source activities

A main statistical analysis was conducted using the commercial software STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test the working hypothesis that the rsEEG source activities may be related to the sex in the Healthy, PDD, and DLB groups.

Three separate ANOVAs were performed (one for each group), with rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). The ANOVAs included the factors Sex (female and male, independent variable), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The clinical unit was used as a covariate. Post-hoc comparisons were conducted using the Duncan test ($p < 0.05$).

Confirmation of the working hypothesis required two criteria: (1) a

statistically significant ANOVA interaction involving the Sex factor ($p < 0.05$) and (2) a post-hoc Duncan test revealing statistically significant ($p < 0.05$ Bonferroni corrected) differences in the rsEEG source activities between the female and male groups.

The results of the main statistical analysis were subjected to the Grubbs test to evaluate the eventual presence of outliers ($p < 0.001$).

2.8. Control statistical analysis of rsEEG source activities

Two control statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test control study hypotheses.

The first control statistical session tested the control study hypothesis that the rsEEG source activities may differ among Healthy, PDD, and DLB groups. An ANOVA was conducted using the rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). The ANOVA included three demographic-matched Healthy ($N = 25$), PDD ($N = 26$), and DLB ($N = 24$) subgroups. The ANOVA used the following factors: Group (Healthy, PDD, and DLB; independent variable), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2), and ROI (frontal, central, parietal, occipital, temporal, and limbic).

The second control statistical session tested the control study hypothesis that the rsEEG source activities may differ among Healthy, PDD, and DLB groups, considering males and females separately. For both male and female subgroups, three separate ANOVAs were performed (one for each band, delta, alpha 2, and alpha 3), with rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). For the males, the ANOVAs included three demographic-matched Healthy-male ($N = 19$), PDD-male ($N = 21$), and DLB-male ($N = 22$) subgroups; for the females, the ANOVAs included three demographic-matched Healthy-female ($N = 12$), PDD-female ($N = 12$), and DLB-female ($N = 22$) subgroups. The ANOVAs included the factors Group (Healthy, PDD, and DLB, independent variable) and ROI (frontal, central, parietal, occipital, temporal, and limbic).

In the control mentioned above analyses, the clinical unit was used as a covariate. Post-hoc comparisons were conducted using the Duncan test ($p < 0.05$).

Confirmation of the two control hypotheses required two criteria: (1) a statistically significant ANOVA interaction including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities among the Healthy vs. PDD vs. DLB groups.

The results of the main statistical analysis were subjected to the Grubbs test to evaluate the eventual presence of outliers ($p < 0.001$).

3. Results

3.1. Demographic, clinical, and rsEEG source markers in healthy-female and healthy-male subgroups

Table 1 summarizes the relevant demographic (i.e., age and

Table 1

Mean values ($\pm$ 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 subgroups of Healthy-female ($N = 24$) and Healthy-male ($N = 25$) participants. Legend: Healthy = cognitively unimpaired older; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

	Female	Male	Statistical analyses
N	24	25	
Age (mean years $\pm$ SE)	70.3 $\pm$ 1.5	71.4 $\pm$ 1.5	n.s. (T-test)
Education (mean years $\pm$ SE)	10.6 $\pm$ 1.1	11.6 $\pm$ 1.0	n.s. (T-test)
MMSE (mean score $\pm$ SE)	27.6 $\pm$ 0.3	27.4 $\pm$ 0.3	n.s. (Mann Whitney U test)

education) and clinical (i.e., MMSE score) information about the Healthy-female ($N = 24$) and Healthy-male ($N = 25$) subgroups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between these subgroups regarding age (t -test), education (t -test), and MMSE score (Mann-Whitney U test). As expected, statistically significant differences were found between the Healthy-female and Healthy-male subgroups for the sex ($p < 0.00001$). On the contrary, no statistically significant differences in age, education, and MMSE score were found between the two subgroups ($p > 0.05$).

The mean TF was 5.5 Hz (± 0.2 SE) in the Healthy-female subgroup and 5.5 Hz (± 0.3 SE) in the Healthy-male subgroup. Furthermore, the mean IAF was 8.4 Hz (± 0.3 SE) in the Healthy-female subgroup and 8.7 Hz (± 0.3 SE) in the Healthy-male subgroup. Two t -tests ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences between the Healthy-female and Healthy-male subgroups regarding TF and IAF. No statistically significant differences were found between the two subgroups ($p > 0.05$).

Fig. 1 shows the mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.6$, $p = 0.001$) between the factors Sex (Healthy-female and Healthy-male; dependent variable) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 7 frequency bands, $p < 0.05/7 = 0.007$) testing showed that the discriminant pattern Healthy-female $>$ Healthy-male was fitted by the rsEEG alpha 2 ($p < 0.001$) and alpha 3 ($p < 0.00001$) source activities. No other effects involving the factor Sex were observed ($p > 0.05$). The data on the basis of these statistical effects were used as an input to compute the size effect by Cohen's d (Cohen, 1977) and the sample size by an alpha level of 0.05 and a desired power of 0.8. The following Cohen's d values (and corresponding sample size for each group) were produced: 0.82 (24 subjects) for the global rsEEG alpha 2 source activity and 0.97 (17 subjects) for the global rsEEG alpha 3 source activity.

The findings mentioned above were not influenced by demographic factors and global cognitive status, as shown by logistic regression models ($p < 0.05$) using the freeware tool Jamovi Version 2.3. These models used age, education, and MMSE score as covariates to assess the association between sex as a predictor and 2 relevant rsEEG source

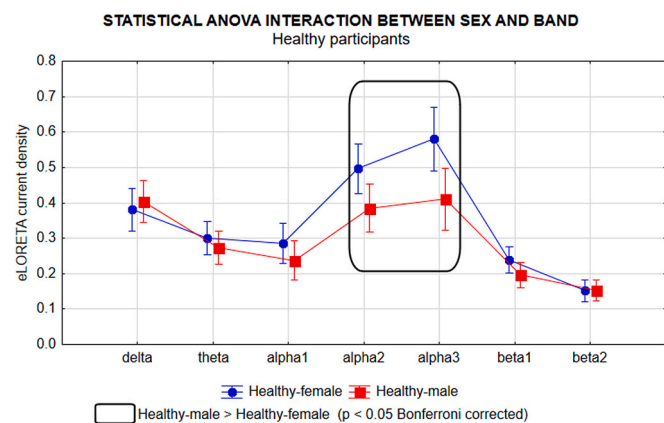


Fig. 1. Mean values ($\pm$ standard error of the mean SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.6$, $p = 0.001$) between the factors Sex (Healthy-female, $N = 24$; and Healthy-male, $N = 25$) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The clinical unit was used as a covariate. The rectangles indicate the frequency bands in which the eLORETA solutions statistically presented a significant difference between Healthy-female and Healthy-male ($p < 0.05$ Bonferroni corrected). Legend: Healthy = cognitively unimpaired older; rsEEG = resting state electroencephalographic.

activities as dependent variables (i.e., global rsEEG alpha 2 and alpha 3 source activities) in the Healthy group. This logistic regression analysis produced the following statistically significant p (< 0.05) and Z values: $p = 0.01$ ($Z = 2.36$) for the global rsEEG alpha 2 source activity and $p = 0.007$ ($Z = 2.71$) for the global rsEEG alpha 3 source activity.

Furthermore, the findings mentioned above were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

3.2. Demographic, clinical, and rsEEG source markers in PDD-female and PDD-male subgroups

Table 2 summarizes the relevant demographic (i.e., age and education) and clinical (i.e., MMSE score, visual hallucination, VH, and Unified Parkinson's disease Rating Scale-III, UPDRS III score; probable REM behavioral disorder, RBD) information about the PDD-female ($N = 13$) and PDD-male ($N = 26$) subgroups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between these subgroups regarding age (t -test), education (t -test), MMSE score (Mann-Whitney U test), VH (Fisher test), UPDRS III score (t -test). As expected, statistically significant differences were found between the PDD-female and PDD-male subgroups for the sex ($p < 0.00001$). On the contrary, no statistically significant differences in age, education, MMSE score, VH, UPDRS III score, and probable RBD were found between the two subgroups ($p > 0.05$).

Table 3 reports the number and the percentages of the PPD-female and PPD-male patients assuming the following drug classes: anti-hypertensive drugs, diabetes drugs, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics, antagonists of N -methyl-D-aspartate receptors (nMDARs), acetylcholinesterase inhibitors (AChEIs), and antiparkinsonian drugs (i.e., levodopa). Seven Fisher tests ($p < 0.05$ uncorrected) were performed to evaluate the presence or absence of statistically significant differences between the PDD-female and PDD-male subgroups regarding the drugs mentioned above. No statistically significant differences were found between the two subgroups ($p > 0.05$). Table 3 also reported the mean values ($\pm$ SE) of levodopa dose (mg/die) in the PPD-female and PPD-male groups. t -test ($p < 0.05$ uncorrected) was performed to evaluate the presence or absence of statistically significant differences between the PDD-female and PDD-male subgroups regarding the daily levodopa dose. No statistically significant difference was found between the two subgroups at $p < 0.05$.

The mean TF was 4.4 Hz (± 0.1 SE) in the PDD-female subgroup and

Table 2

Mean values ($\pm$ SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of PDD-female ($N = 13$) and PDD-male ($N = 26$) participants. Legend: PDD = Parkinson's Disease Dementia; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation; VH = visual hallucination; UPDRS III = Unified Parkinson's disease Rating Scale-III; RBD = REM behavioral disorder.

	Female	Male	Statistical analyses
N	13	26	–
Age (mean years $\pm$ SE)	74.1 $\pm$ 1.7	73.0 $\pm$ 1.3	n.s. (T -test)
Education (mean years $\pm$ SE)	8.7 $\pm$ 1.4	9.7 $\pm$ 0.8	n.s. (T -test)
MMSE (mean score $\pm$ SE)	16.4 $\pm$ 1.4	17.5 $\pm$ 0.7	n.s. (Mann Whitney U test)
VH (%)	62	73	n.s. (Fisher test)
UPDRS III (mean score $\pm$ SE)	42.1 $\pm$ 4.6	39.7 $\pm$ 5.1	n.s. (T -Test)
Probable RBD (%)	55	60	n.s. (Fisher test)

Table 3

Number and the percentages of the PDD-female (N = 13) and PDD-male (N = 26) participants assuming the following drug classes: anti-hypertensive drugs, diabetes drugs, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics, antagonists of *N*-methyl-D-aspartate receptors (aNMDARs), acetylcholinesterase inhibitors (AChEIs), and antiparkinsonian drugs (i.e., levodopa). The mean values ($\pm$ SE) of levodopa dose (mg/die) are also reported. Furthermore, the results of statistical comparisons ($p < 0.05$ uncorrected) in the subgroups of PDD-female and PDD-male participants are stated. No statistically significant difference was found between the two subgroups at $p < 0.05$. Legend: PDD = Parkinson's Disease Dementia.

	Female	Male	Statistical analyses
High blood pressure drugs (N; %)	2; 15.4	4; 15.4	n.s. (Fisher test)
Diabetes drugs (N; %)	0; 0	3; 11.5	n.s. (Fisher test)
Selective serotonin reuptake inhibitors (SSRIs; N; %)	0; 0	2; 7.7	n.s. (Fisher test)
Anxiolytics (N; %)	0; 0	2; 7.7	n.s. (Fisher test)
Antipsychotics (N; %)	2; 15.4	3; 11.5	n.s. (Fisher test)
Antagonists of <i>N</i> -methyl-D-aspartate receptors (aNMDARs; N; %)	4; 30.8	3; 11.5	n.s. (Fisher test)
Acetylcholinesterase inhibitors (AChEIs; N; %)	3; 23	11; 42.3	n.s. (Fisher test)
Dopamine agonists (N; %)	5; 38.4	11; 42.3	n.s. (Fisher test)
Monoamine oxidase B (MAO-B) inhibitors (N; %)	2; 15.4	4; 15.4	n.s. (Fisher test)
Levodopa (N; %)	13; 100	23; 100	n.s. (Fisher test)
Levodopa dose (mg; mean $\pm$ SE)	467 $\pm$ 82	584 $\pm$ 54	n.s. (T-test)

4.8 Hz ($\pm$ 0.3 SE) in the PDD-male subgroup. Furthermore, the mean IAF was 7.0 Hz ($\pm$ 0.3 SE) in the PDD-female subgroup and 6.7 Hz ($\pm$ 0.3 SE) in the PDD-male subgroup. Two *t*-tests ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences between the PDD-female and PDD-male subgroups regarding TF and IAF. No statistically significant differences were found between the two subgroups ($p > 0.05$).

Fig. 2 shows the mean values ($\pm$ SE, log-10 transformed) of rsEEG

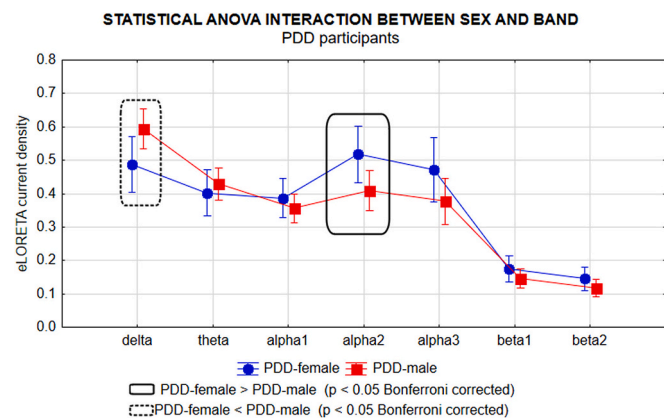


Fig. 2. Mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 6.1, p = 0.00001$) between the factors Sex (PDD-female, N = 13; and PDD-male, N = 26) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The clinical unit was used as a covariate. The rectangles indicate the frequency bands in which the eLORETA solutions statistically presented a significant difference between PDD-female and PDD-male ($p < 0.05$ Bonferroni corrected). Legend: PDD = cognitively unimpaired older; rsEEG = resting state electroencephalographic.

source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 6.1, p = 0.00001$) between the factors Sex (PDD-female and PDD-male; dependent variable) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 7 frequency bands, $p < 0.05/7 = 0.007$) testing showed that (1) the discriminant pattern PDD-female < PDD-male was fitted by the rsEEG delta ($p < 0.005$) source activity and (2) the discriminant pattern PDD-female > PDD-male was fitted by the rsEEG alpha 2 ($p < 0.005$) source activity. No other effects involving the factor Sex were observed ($p > 0.05$). The data on the basis of these statistical effects were used as an input to compute the size effect by Cohen's *d* and the sample size as described above. The following Cohen's *d* values (and corresponding sample size for each group) were produced: -1.69 (7 subjects) for the global rsEEG delta source activity and 0.63 (40 subjects) for the global rsEEG alpha 2 source activity.

The findings mentioned above were not due to demographic factors, global cognitive status, and dopaminergic therapy, as shown by logistic regression models ($p < 0.05$). These models used age, education, MMSE score, and levodopa dose as covariates to assess the association between sex as a predictor and 2 relevant rsEEG source activities as dependent variables (i.e., global rsEEG delta and alpha 2 source activities) in the PDD group. The logistic regression analysis produced the following statistically significant p (< 0.05) and Z values: $p = 0.03$ ($Z = -2.1$) for the global rsEEG delta source activity and $p = 0.04$ ($Z = 2.0$) for the global rsEEG alpha 2 source activity.

Furthermore, the findings mentioned above were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

3.3. Demographic, clinical, and rsEEG source markers in DLB-female and DLB-male subgroups

Table 4 summarizes the relevant demographic (i.e., age and education) and clinical (i.e., MMSE score, VH, UPDRS III score, and probable RBD) information about the DLB-female (N = 15) and DLB-male (N = 23) subgroups, together with the results of the statistical analyses computed to evaluate the presence or absence of statistically significant differences between these subgroups regarding age (*t*-test), education (*t*-test), MMSE score (Mann-Whitney *U* test), VH (Fisher test), and UPDRS III score (*t*-test). As expected, statistically significant differences were found between the DLB-female and DLB-male subgroups for the sex ($p < 0.00001$). On the contrary, no statistically significant differences in age, education, MMSE score, VH, UPDRS III score, and probable RBD were

Table 4

Mean values ($\pm$ SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of DLB-female (N = 15) and DLB-male (N = 23) participants. Legend: DLB = Lewy Body Dementia; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation; VH = visual hallucination; UPDRS III = Unified Parkinson's disease Rating Scale-III; RBD = REM behavioral disorder.

	Female	Male	Statistical analyses
N	15	23	–
Age (mean years $\pm$ SE)	77.9 $\pm$ 1.5	76.0 $\pm$ 2.0	n.s. (<i>t</i> -test)
Education (mean years $\pm$ SE)	6.7 $\pm$ 0.8	7.9 $\pm$ 0.8	n.s. (<i>t</i> -test)
MMSE (mean score $\pm$ SE)	19.8 $\pm$ 1.5	19.6 $\pm$ 1.3	n.s. (Mann Whitney U test)
VH (%)	60	77	n.s. (Fisher test)
UPDRS III (mean score $\pm$ SE)	16.0 $\pm$ 4.6	15.3 $\pm$ 2.1	n.s. (<i>t</i> -test)
Probable RBD (%)	53	68	n.s. (Fisher test)

found between the two subgroups ($p > 0.05$).

Table 5 reports the number and the percentages of the DLB-female and DLB-male patients assuming the following drug classes: anti-hypertensive drugs, diabetes drugs, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics, antagonists of *N*-methyl-D-aspartate receptors (aNMDARs), acetylcholinesterase inhibitors (AChEIs), and antiparkinsonian drugs (i.e., levodopa). Seven Fisher tests ($p < 0.05$ uncorrected) were performed to evaluate the presence or absence of statistically significant differences between the DLB-female and DLB-male subgroups regarding the drugs mentioned above. No statistically significant differences were found between the two subgroups ($p > 0.05$). **Table 5** also reported the mean values ($\pm$ SE) of levodopa dose (mg/die) in the DLB-female and DLB-male groups. *t*-test ($p < 0.05$ uncorrected) was performed to evaluate the presence or absence of statistically significant differences between the PDD-female and PDD-male subgroups regarding the daily levodopa dose. No statistically significant difference was found between the two subgroups at $p < 0.05$.

The mean TF was 4.9 Hz (± 0.2 SE) in the DLB-female subgroup and 4.8 Hz (± 0.2 SE) in the DLB-male subgroup. Furthermore, the mean IAF was 7.7 Hz (± 0.3 SE) in the DLB-female subgroup and 7.1 Hz (± 0.2 SE) in the DLB-male subgroup. Two *t*-tests ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences between the DLB-female and DLB-male subgroups regarding TF and IAF. No statistically significant differences were found between the two subgroups ($p > 0.05$).

Fig. 3 shows the mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 2.6$, $p = 0.00001$) among the factors Sex (PDD-female and PDD-male), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The Duncan planned post-hoc

($p < 0.05$ Bonferroni correction for 7 frequency bands $\times 6$ ROI, $p < 0.05/42 = 0.0011$) testing showed that (1) the discriminant pattern DLB-female $<$ DLB-male was fitted by central ($p < 0.0005$) and parietal ($p < 0.005$) rsEEG delta source activities and (2) the discriminant pattern DLB-female $>$ DLB-male was fitted by occipital ($p < 0.0001$) and temporal ($p < 0.0001$) rsEEG alpha 2 source activities as well as parietal ($p < 0.0005$), occipital ($p < 0.00001$), and temporal ($p < 0.00005$) rsEEG alpha 3 source activities. The data based on these statistical effects were used as an input to compute the size effect by Cohen's *d* and the sample size as described above. The analysis produced the following Cohen's *d* values (and corresponding sample size for each group): -0.89 (20 subjects) for the central rsEEG delta source activity, -0.71 (32 subjects) for the parietal rsEEG delta source activity, 0.82 (24 subjects) for the occipital rsEEG alpha 2 source activity, 0.77 (27 subjects) for the temporal rsEEG alpha 2 source activity, 0.64 (39 subjects) for the parietal rsEEG alpha 3 source activity, 1.22 (11 subjects) for the occipital rsEEG alpha 3 source activity, and 0.88 (21 subjects) for the temporal rsEEG alpha 3 source activity.

Furthermore, there was another effect. **Fig. 4** shows the mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.0$, $p = 0.007$) between the factors Sex (DLB-female and DLB-male; independent variable) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 7 frequency bands, $p < 0.05/7 = 0.007$) testing showed that the discriminant pattern DLB-female $>$ DLB-male was fitted by rsEEG alpha 3 source activity ($p < 0.001$). The data on the basis of these statistical effects were used as an input to compute the size effect by Cohen's *d* and the sample size as described above. The analysis produced the following Cohen's *d* value (and corresponding sample size for each group): 0.84 (23 subjects) for the global rsEEG alpha 3 source activity.

The findings mentioned above were not due to demographic factors, global cognitive status, and dopaminergic therapy, as shown by logistic regression models ($p < 0.05$). These models used age, education, MMSE score, and levodopa dose as covariates to assess the association between sex as a predictor and 7 relevant rsEEG source activities as dependent variables (i.e., central delta, parietal delta, occipital alpha 2, temporal alpha 2, parietal alpha 3, occipital alpha 3, temporal alpha 2, and global alpha 3 source activities from rsEEG rhythms) in the DLB group. The logistic regression analysis produced the following statistically significant p (< 0.05) and Z values: $p = 0.02$ ($Z = -2.3$) for the central rsEEG delta source activity, $p = 0.02$ ($Z = 2.3$) for the occipital rsEEG alpha 2 source activity, $p = 0.03$ ($Z = 2.2$) for the temporal rsEEG alpha 2 source activity, $p = 0.007$ ($Z = 2.7$) for the occipital rsEEG alpha 3 source activity, $p = 0.02$ ($Z = 2.4$) for the temporal rsEEG alpha 2 source activity, and $p = 0.03$ ($Z = 2.2$) for the global rsEEG alpha 3 source activity.

Furthermore, the findings mentioned above were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

3.4. Control analyses

Two sessions of control analyses were performed.

The first session aimed at testing the control hypothesis that the present rsEEG delta and alpha 2–3 source activities showed statistically significant differences among the Healthy, DLB, and PDD groups ($p < 0.05$). To test this hypothesis, we selected three subgroups of Healthy, DLB, and PDD participants matched for age, sex, and education attainment. Furthermore, the two subgroups of DLB and PDD participants were matched for global cognitive status (i.e., MMSE score; see *Supplementary Materials, Control analyses* for a detailed description of participants' selection). **Table 6** summarizes the relevant demographic (i.e., age, education, and sex) and clinical (i.e., MMSE score) information about the demographic-matched Healthy ($N = 25$), PDD ($N = 26$), and

Table 5

Number and the percentages of the DLB-female ($N = 15$) and DLB-male ($N = 23$) participants assuming the following drug classes: anti-hypertensive drugs, diabetes drugs, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics, antagonists of *N*-methyl-D-aspartate receptors (aNMDARs), acetylcholinesterase inhibitors (AChEIs), and antiparkinsonian drugs (i.e., levodopa, dopamine agonists and monoamine oxidase B, MAO-B, inhibitors). The mean values ($\pm$ SE) of levodopa dose (mg/die) are also reported. Furthermore, the results of statistical comparisons ($p < 0.05$ uncorrected) in the subgroups of PDD-female and PDD-male participants are stated. No statistically significant difference was found between the two subgroups at $p < 0.05$. Legend: DLB = Lewy Body Dementia.

	Female	Male	Statistical analyses
High blood pressure drugs (N; %)	6; 40	10; 43.5	n.s. (Fisher test)
Diabetes drugs (N; %)	4; 26.7	13; 56.5	n.s. (Fisher test)
Selective serotonin reuptake inhibitors (SSRIs; N; %)	7; 46.7	6; 26.1	n.s. (Fisher test)
Anxiolytics (N; %)	0; 0	1; 4.3	n.s. (Fisher test)
Antipsychotics (N; %)	3; 20	2; 11.5	n.s. (Fisher test)
Antagonists of <i>N</i> -methyl-D-aspartate receptors (aNMDARs; N; %)	4; 26.7	4; 17.4	n.s. (Fisher test)
Acetylcholinesterase inhibitors (AChEIs; N; %)	11; 73.3	18; 78.2	n.s. (Fisher test)
Dopamine agonists (N; %)	2; 13.3	3; 13	n.s. (Fisher test)
Monoamine oxidase B (MAO-B) inhibitors (N; %)	3; 20	3; 13	n.s. (Fisher test)
Levodopa (N; %)	9; 60	9; 40	n.s. (Fisher test)
Levodopa dose (mg; mean $\pm$ SE)	138 $\pm$ 55	117 $\pm$ 45	n.s. (T-test)

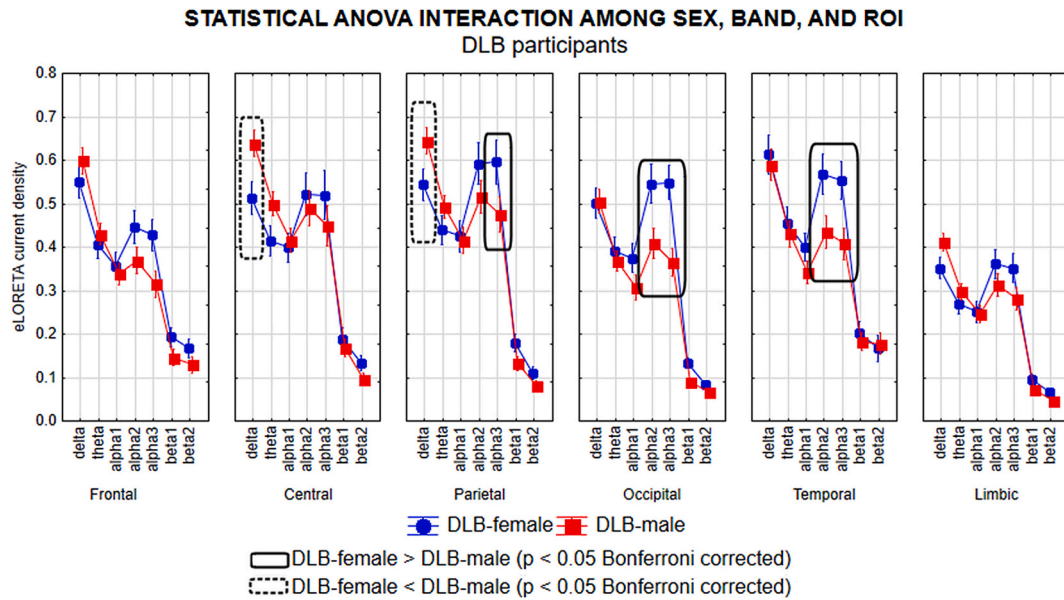


Fig. 3. Mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 2.6$, $p = 0.00001$) among the factors Sex (DLB-female, $N = 15$; and DLB-male, $N = 23$), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2) and ROI (frontal, central, parietal, occipital, temporal, and limbic). The clinical unit was used as a covariate. The rectangles indicate the frequency bands and ROIs in which the eLORETA solutions statistically presented a significant difference between DLB-female and DLB-male ($p < 0.05$ Bonferroni corrected). Legend: DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic; ROI = region of interest.

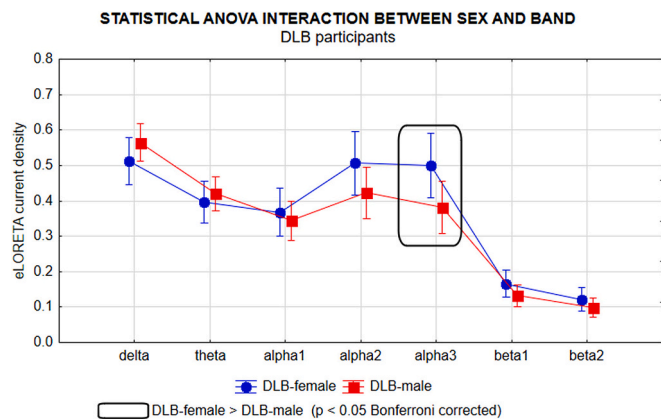


Fig. 4. Mean values ($\pm$ standard error of the mean SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.1$, $p = 0.007$) between the factors Sex (DLB-female, $N = 15$; and DLB-male, $N = 23$) and Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, and beta 2). The clinical unit was used as a covariate. The rectangles indicate the frequency bands in which the eLORETA solutions statistically presented a significant difference between DLB-female and DLB-male ($p < 0.05$ Bonferroni corrected). Legend: DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic.

DLB ($N = 24$) subgroups, together with the results of the statistical analyses ($p < 0.05$) computed to evaluate the presence or absence of statistically significant differences between these subgroups for age (ANOVA), sex (Freeman Halton test), education attainment (ANOVA), and MMSE score (Kruskal-Wallis ANOVA). As expected, statistically significant differences were found between the Healthy vs. PDD and DLB subgroups for the MMSE score ($p < 0.00001$). On the contrary, no statistically significant differences in age, education, and sex were found among the three subgroups ($p > 0.05$). Furthermore, no statistically significant difference in MMSE score was found among the PDD and DLB subgroups ($p > 0.05$).

As a further step, we compared the mean TF and IAF among the

Table 6

Mean values ($\pm$ SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of matched Healthy ($N = 25$), PDD ($N = 26$), and DLB ($N = 24$) participants. Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; M/F = males/females; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

	Healthy	PDD	DLB	Statistical analyses
N	25	26	24	–
Age (mean years $\pm$ SE)	72.6 $\pm$ 1.4	73.0 $\pm$ 1.3	74.5 $\pm$ 1.6	n.s. (ANOVA)
Sex (F/M)	11/14	6/20	7/17	n.s. (Freeman Halton test)
Education (mean years $\pm$ SE)	9.7 $\pm$ 0.9	8.9 $\pm$ 0.7	7.9 $\pm$ 0.6	n.s. (ANOVA)
MMSE (mean score $\pm$ SE)	27.7 $\pm$ 0.3	18.1 $\pm$ 0.7	18.8 $\pm$ 1.0	$p < 0.0001$ (Kruskal-Wallis test)

above three subgroups. The mean TF was 5.5 Hz (± 0.2 SE) in the Healthy subgroup, 4.4 Hz (± 0.1 SE) in the PDD subgroup, and 4.9 Hz (± 0.2 SE) in the DLB subgroup. Furthermore, the mean IAF was 8.6 Hz (± 0.3 SE) in the Healthy subgroup, 6.5 Hz (± 0.2 SE) in the PDD subgroup, and 7.4 Hz (± 0.2 SE) in the DLB subgroup. Two ANOVAs ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences among the Healthy, PDD, and DLB subgroups regarding TF and IAF. The ANOVAs showed the following statistically significant effects: (1) the mean TF was greater ($F = 11.8$, $p < 0.0001$) in the Healthy subgroup than in the PDD and DLB subgroups ($p < 0.005$); (2) the mean IAF was greater ($F = 26.4$, $p < 0.0001$) in the Healthy subgroup than in the PDD and DLB subgroups ($p < 0.0005$); it was also greater in the DLB subgroup than in the PDD subgroup ($p < 0.005$).

Fig. 5 shows the mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.4$, $p = 0.00001$) among the factors Group (Healthy, PDD, and DLB; independent

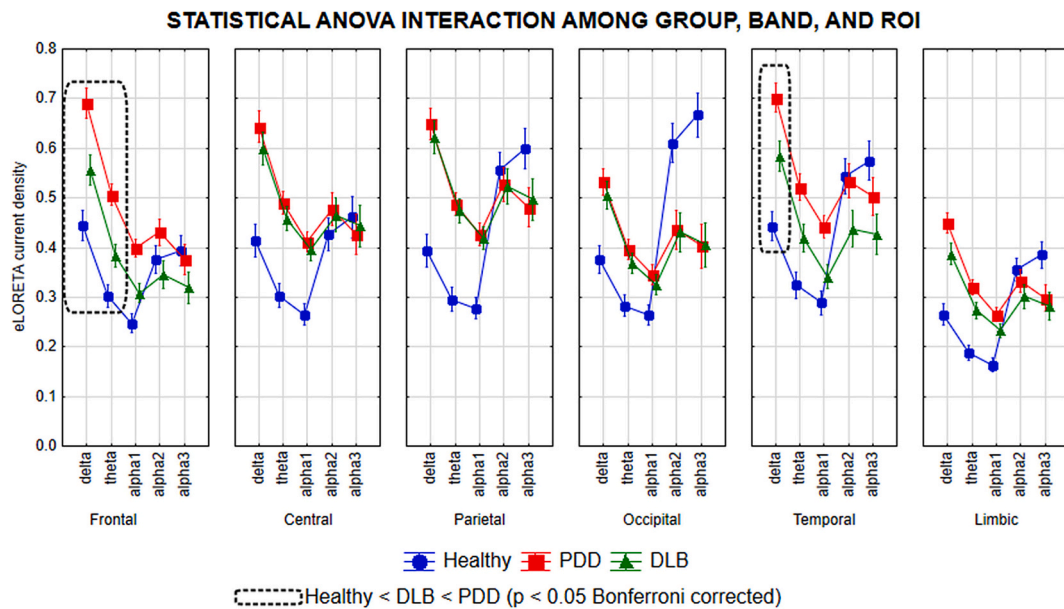


Fig. 5. Mean values ($\pm$ SE, log-10 transformed) of rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 3.4$, $p = 0.00001$) among the factors Group (Healthy, $N = 25$; PDD, $N = 26$; and DLB, $N = 24$), Band (delta, theta, alpha 1, alpha 2, and alpha 3) and ROI (frontal, central, parietal, occipital, temporal, and limbic). The clinical unit was used as a covariate. The rectangles indicate the frequency bands and ROIs in which the eLORETA solutions statistically presented a significant difference among the matched Healthy, PDD, and DLB participants ($p < 0.05$ Bonferroni corrected). Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic; ROI = region of interest.

variable), Band (delta, theta, alpha 1, alpha 2, and alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Notably, the profile and magnitude of the rsEEG source activities in the Healthy, PDD, and DLB groups differed across the groups and ROIs. Specifically, the Nold group showed rsEEG alpha 2 and alpha 3 sources with maximum activities distributed in the parietal and occipital regions. The rsEEG alpha 1, theta, and delta sources showed moderate activities when compared with those of rsEEG alpha 2 and alpha 3 sources. Compared to the Healthy group, the PDD and DLB groups showed a substantial decrease in the posterior (i.e., parietal and occipital) rsEEG alpha 2 and alpha 3 source activities. Furthermore, compared to the Healthy group, the PDD and DLB groups showed a substantial increase in widespread rsEEG alpha 1, theta, and delta source activities. Finally, the increase in frontal-temporal rsEEG delta and theta source activities was higher in the PDD than in the DLB group. These results support the idea that distinct spatial-frequency patterns of cortical source activities in these groups generate the scalp EEG rhythms.

The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 5 frequency bands $\times$ 6 ROIs, $p < 0.05/30 = 0.0016$) testing showed that (1) the discriminant pattern Healthy < DLB < PDD was fitted by central ($p < 0.00005$) and temporal ($p < 0.0005$) rsEEG delta source activities as well as frontal ($p < 0.0005$) rsEEG theta source activities. The data based on these statistical effects were used as an input to compute the size effect by Cohen's d and the sample size as described above. The analysis produced the following Cohen's d value (and corresponding sample size for each group): (1) in the comparison between the Healthy and PDD groups, -1.64 (6 subjects) for the frontal rsEEG delta source activity, -1.91 (5 subjects) for the temporal rsEEG delta source activity, and -1.78 (5 subjects) for the frontal rsEEG theta source activity; (2) in the comparison between the Healthy and DLB groups, -0.75 (28 subjects) for the frontal rsEEG delta source activity, -0.94 (18 subjects) for the temporal rsEEG delta source activity, and -0.75 (28 subjects) for the frontal rsEEG theta source activity; and (3) in the comparison between the PDD and DLB groups, 0.97 (18 subjects) for the frontal rsEEG delta source activity, 0.79 (26 subjects) for the temporal rsEEG delta source activity, and 1.15 (12 subjects) for the frontal rsEEG theta source

activity.

Furthermore, the Duncan planned post-hoc testing showed that: (1) the discriminant pattern Healthy < DLB and PDD was fitted by central ($p < 0.00001$), parietal ($p < 0.00001$), occipital ($p < 0.0001$), and limbic ($p < 0.0005$) rsEEG delta source activities as well as central ($p < 0.0001$) theta rsEEG source activities and central ($p < 0.0001$) and parietal ($p < 0.0001$) rsEEG alpha 1 source activities; and (2) the discriminant pattern Healthy > DLB and PDD was fitted by occipital ($p < 0.00001$) rsEEG alpha 2 source activities as well as parietal ($p < 0.0001$) and occipital ($p < 0.00001$) rsEEG alpha 3 source activities.

These findings were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

The second session aimed at testing the control hypothesis that the present rsEEG delta and alpha 2–3 source activities showed statistically significant differences among the subgroups of Healthy, DLB, and PDD males ($p < 0.05$) and the subgroups of Healthy, DLB, and PDD females.

We selected three subgroups of Healthy, DLB, and PDD male participants matched for age education attainment. Furthermore, the two subgroups of DLB and PDD males were matched for global cognitive status (i.e., MMSE score; see *Supplementary Materials, Control analyses* for a detailed description of participants' selection). Table 7 summarizes the relevant demographic (i.e., age, and education) and clinical (i.e., MMSE score) information about the demographic-matched Healthy-male ($N = 19$), PDD-male ($N = 22$), and DLB-male ($N = 21$) subgroups, together with the results of the statistical analyses ($p < 0.05$) computed to evaluate the presence or absence of statistically significant differences between these subgroups for age (ANOVA), education attainment (ANOVA), and MMSE score (Kruskal-Wallis ANOVA). As expected, statistically significant differences were found between the Healthy-male vs. PDD-male and DLB-male subgroups for the MMSE score ($p < 0.00001$). On the contrary, no statistically significant differences in age and education were found among the three male subgroups ($p > 0.05$). Furthermore, no statistically significant difference in MMSE score was found among the PDD and DLB male subgroups ($p > 0.05$).

The mean TF was 5.4 Hz (± 0.2 SE) in the Healthy-male subgroup,

Table 7

Mean values ($\pm$ SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of matched Healthy-male ($N = 19$), PDD-male ($N = 22$), and DLB-male ($N = 21$) participants. Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

	Healthy	PDD	DLB	Statistical analyses
N	19	22	21	–
Age (mean years $\pm$ SE)	73.1 $\pm$ 1.9	73.8 $\pm$ 1.2	75.6 $\pm$ 2.1	n.s. (ANOVA)
Education (mean years $\pm$ SE)	11.0 $\pm$ 0.9	9.6 $\pm$ 0.8	8.4 $\pm$ 0.8	n.s. (ANOVA)
MMSE (mean score $\pm$ SE)	27.5 $\pm$ 0.4	17.7 $\pm$ 0.7	19.6 $\pm$ 1.1	$p < 0.0001$ (Kruskal-Wallis test)

4.7 Hz (± 0.2 SE) in the PDD-male subgroup, and 4.8 Hz (± 0.2 SE) in the DLB-male subgroup. Furthermore, the mean IAF was 8.6 Hz (± 0.3 SE) in the Healthy-male subgroup, 6.7 Hz (± 0.2 SE) in the PDD-male subgroup, and 7.0 Hz (± 0.2 SE) in the DLB-male subgroup. Two ANOVAs ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences among the Healthy-male, PDD-male, and DLB-male subgroups regarding TF and IAF. The ANOVAs showed the following statistically significant effect: the mean IAF was greater ($F = 14.6$, $p < 0.0001$) in the Healthy-male subgroup than in the PDD-male and DLB-male subgroups ($p < 0.0005$).

For the delta frequency band, the ANOVA showed a statistically significant main effect ($F = 14.1$, $p = 0.0001$; Fig. 6) for the factor Group (Healthy-male, PDD-male, and DLB-male; independent variable), unveiling that the widespread rsEEG delta source activity was lower in the Healthy-male subgroup compared to the DLB-male and PDD-male subgroups ($p < 0.0001$). The data on the basis of these statistical effects were used as an input to compute the size effect by Cohen's d and the sample size as described above. The analysis produced the following Cohen's d values (and corresponding sample size for each group): (1) in the comparison between the Healthy and PDD male groups, -1.49 (8 subjects) for the global rsEEG delta source activity; and (2) in the comparison between the Healthy and DLB male groups, -1.35 (9 subjects) for the global rsEEG delta source activity.

For the alpha 2 frequency band, the ANOVA did not show statistically significant results including the factor Group ($p > 0.05$).

For the alpha 3 frequency band, the ANOVA showed a statistically significant interaction effect ($F = 4.8$, $p = 0.0001$; Fig. 7) among the factors Group (Healthy-male, PDD-male, and DLB-male; independent

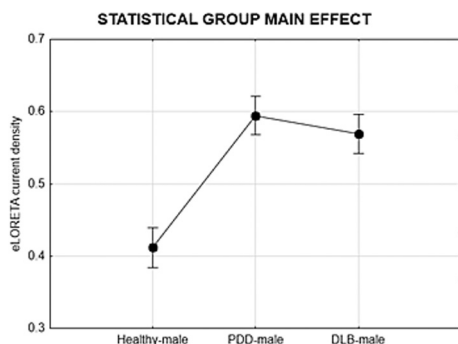


Fig. 6. Mean values ($\pm$ SE, log-10 transformed) of delta rsEEG source activities (normalized eLORETA current density) relative to a statistically significant main effect ($F = 14.1$, $p = 0.0001$) for the factors Group (Healthy-male, $N = 19$; PDD-male, $N = 22$; and DLB-male, $N = 21$). The clinical unit was used as a covariate. Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic.

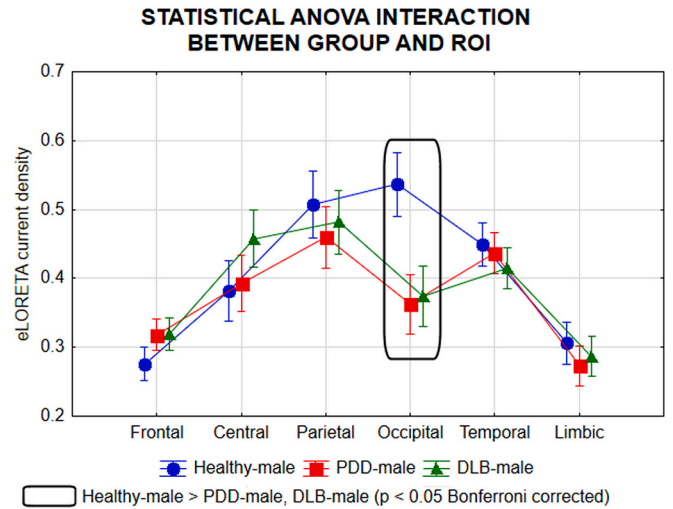


Fig. 7. Mean values ($\pm$ SE, log-10 transformed) of alpha 3 rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 4.8$, $p = 0.0001$) between the factors Group (Healthy-male, $N = 19$; PDD-male, $N = 22$; and DLB-male, $N = 21$), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The clinical unit was used as a covariate. The rectangles indicate the ROI in which the eLORETA solutions statistically presented a significant difference among the matched Healthy-male, PDD-male, and DLB-male participants ($p < 0.05$ Bonferroni corrected). Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic; ROI = region of interest.

variable) and ROI (frontal, central, parietal, occipital, temporal, and limbic). The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 6 ROIs, $p < 0.05/6 = 0.0083$) testing showed that the discriminant pattern Healthy-male > DLB-male and PDD-male was fitted by occipital rsEEG alpha 3 source activities ($p < 0.005$). The data based on these statistical effects were used as an input to compute the size effect by Cohen's d and the sample size as described above. The analysis produced the following Cohen's d values (and corresponding sample size for each group): (1) in the comparison between the Healthy and PDD male groups, 0.82 (24 subjects) for the occipital rsEEG alpha 3 source activity; and (2) in the comparison between the Healthy and DLB male groups, 0.75 (28 subjects) for the occipital rsEEG alpha 3 source activity.

These findings were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

The above procedure was repeated for three subgroups of the Healthy, DLB, and PDD females, matched for age education attainment. Furthermore, the two subgroups of DLB and PDD females were matched for global cognitive status (i.e., MMSE score; see *Supplementary Materials, Control analyses* for a detailed description of participants' selection). Table 8 summarizes the relevant demographic (i.e., age and education) and clinical (i.e., MMSE score) information about the demographic-matched Healthy-female ($N = 11$), PDD-female ($N = 12$), and DLB-female ($N = 12$) subgroups, together with the results of the statistical analyses ($p < 0.05$) computed to evaluate the presence or absence of statistically significant differences between these subgroups for age (ANOVA), education attainment (ANOVA), and MMSE score (Kruskal-Wallis ANOVA). As expected, statistically significant differences were found between the Healthy-female vs. PDD-female and DLB-female subgroups for the MMSE score ($p < 0.00001$). On the contrary, no statistically significant differences in age and education were found among the three female subgroups ($p > 0.05$). Furthermore, no statistically significant difference in MMSE score was found among the PDD and DLB female subgroups ($p > 0.05$).

The mean TF was 5.7 Hz (± 0.3 SE) in the Healthy-female subgroup,

Table 8

Mean values ($\pm$ SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the subgroups of matched Healthy-female ($N = 11$), PDD-female ($N = 12$), and DLB-female ($N = 12$) participants. Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; n.s. = not significant ($p > 0.05$); MMSE = Mini-Mental State Evaluation.

	Healthy	PDD	DLB	Statistical analyses
N	11	12	12	–
Age (mean years $\pm$ SE)	74.5 $\pm$ 1.4	74.3 $\pm$ 1.9	76.3 $\pm$ 1.5	n.s. (ANOVA)
Education (mean years $\pm$ SE)	9.9 $\pm$ 1.3	8.3 $\pm$ 1.4	6.8 $\pm$ 1.0	n.s. (ANOVA)
MMSE (mean score $\pm$ SE)	27.9 $\pm$ 0.2	16.5 $\pm$ 1.5	18.2 $\pm$ 1.7	$p < 0.0001$ (Kruskal-Wallis test)

4.4 Hz ($\pm$ 0.1 SE) in the PDD-female subgroup, and 4.9 Hz ($\pm$ 0.2 SE) in the DLB-female subgroup. Furthermore, the mean IAF was 8.6 Hz ($\pm$ 0.4 SE) in the Healthy-female subgroup, 7.0 Hz ($\pm$ 0.3 SE) in the PDD-female subgroup, and 7.5 Hz ($\pm$ 0.3 SE) in the DLB-female subgroup. Two ANOVAs ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences among the Healthy-female, PDD-female, and DLB-female subgroups regarding TF and IAF. The ANOVAs showed the following statistically significant effects: (1) the mean TF was greater ($F = 7.8$, $p < 0.001$) in the Healthy subgroup than in the PDD and DLB subgroups ($p < 0.01$); (2) the mean IAF was greater ($F = 5.9$, $p < 0.01$) in the Healthy subgroup than in the PDD and DLB subgroups ($p < 0.05$).

For the delta frequency band, the ANOVA showed a statistically significant main effect ($F = 9.8$, $p = 0.0005$; Fig. 8) for the factor Group (Healthy-female, PDD-female, and DLB-female; independent variable), unveiling that the widespread rsEEG delta source activity was lower in the Healthy-female subgroup compared to the DLB-female and PDD-female subgroups ($p < 0.005$). The data based on these statistical effects were used as an input to compute the size effect by Cohen's d and the sample size as described above. The analysis produced the following Cohen's d values (and corresponding sample size for each group): (1) in the comparison between the Healthy and PDD female groups, -1.18 (12 subjects) for the global rsEEG delta source activity; and (2) in the comparison between the Healthy and DLB female groups, -1.71 (6 subjects) for the global rsEEG delta source activity.

For the alpha 2 frequency band, the ANOVA did not show statistically significant results including the factor Group ($p > 0.05$).

For the alpha 3 frequency band, the ANOVA showed a statistically

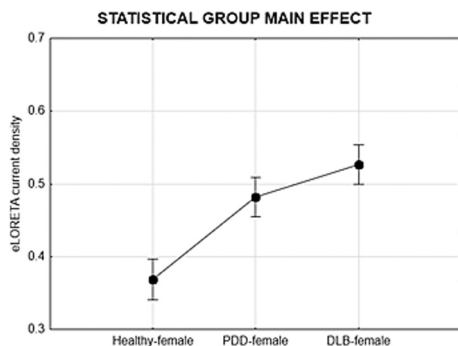


Fig. 8. Mean values ($\pm$ SE, log-10 transformed) of delta rsEEG source activities (normalized eLORETA current density) relative to a statistically significant main effect ($F = 9.8$, $p = 0.0005$) for the factors Group (Healthy-female, $N = 11$; PDD-female, $N = 12$; and DLB-female, $N = 12$). The clinical unit was used as a covariate. Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic.

significant interaction effect ($F = 2.7$, $p = 0.005$; Fig. 9) among the factors Group (Healthy-female, PDD-female, and DLB-female; independent variable) and ROI (frontal, central, parietal, occipital, temporal, and limbic). The Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 6 ROIs, $p < 0.05/6 = 0.0083$) testing showed that the discriminant pattern Healthy-female $>$ DLB-female and PDD-female was fitted by occipital rsEEG alpha 3 source activities ($p < 0.005$). The data based on these statistical effects were used as an input to compute the size effect by Cohen's d and the sample size as described above. The analysis produced the following Cohen's d values (and corresponding sample size for each group): (1) in the comparison between the Healthy and PDD female groups, 1.19 (12 subjects) for the occipital rsEEG alpha 3 source activity; and (2) in the comparison between the Healthy and DLB female groups, 1.33 (9 subjects) for the occipital rsEEG alpha 3 source activity.

These findings were not due to outliers from individual normalized eLORETA current densities (log 10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

4. Discussion

In this exploratory study, we tested whether cortical sources of rsEEG delta and alpha rhythms underpinning the quiet vigilance dysregulation in DLB and PDD patients may vary depending on the sex factor. The hypothesis stems from the higher prevalence of males than females in those patients (Savica et al., 2013a, 2013b; Irwin et al., 2017; Lemstra et al., 2017; Patel and Kompoliti, 2023; Ben-Shlomo et al., 2024; Gro-tewold and Albin, 2024) and the sensitivity of rsEEG rhythms to the sex factor (Veldhuizen et al., 1993; Duffy et al., 1993; Wada et al., 1994; Babiloni et al., 2022). The different disease prevalences in males and females may unveil sex-dependent neuroprotective/compensatory neurophysiological mechanisms in PDD and DLB patients, reflected by rsEEG rhythms.

In healthy controls, as expected from previous literature, we found that the sex factor significantly affected widespread rsEEG alpha source

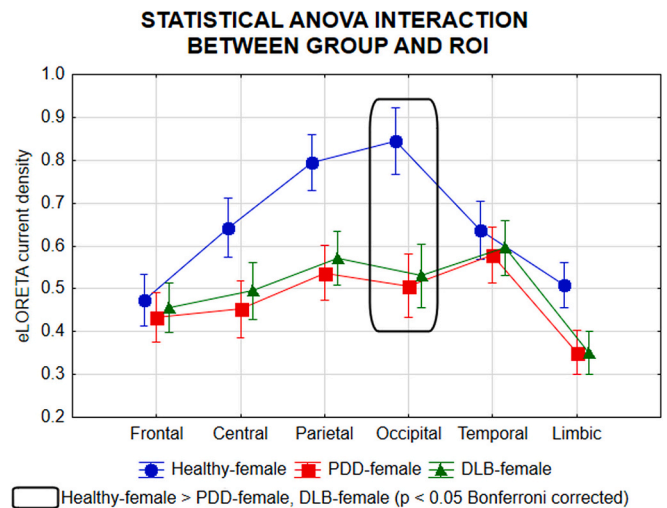


Fig. 9. Mean values ($\pm$ SE, log-10 transformed) of alpha 3 rsEEG source activities (normalized eLORETA current density) relative to a statistically significant ANOVA interaction effect ($F = 2.4$, $p = 0.005$) between the factors Group (Healthy-female, $N = 11$; PDD-female, $N = 12$; and DLB-female, $N = 12$), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The clinical unit was used as a covariate. The rectangles indicate the ROI in which the eLORETA solutions statistically presented a significant difference among the matched Healthy-female, PDD-female, and DLB-female participants ($p < 0.05$ Bonferroni corrected). Legend: Healthy = cognitively unimpaired older; PDD = Parkinson's Disease Dementia; DLB = Lewy Body Dementia; rsEEG = resting state electroencephalographic; ROI = region of interest.

activities estimated in the healthy participants. Specifically, the females exhibited greater widespread rsEEG alpha source activities compared to the males, in agreement with previous research evidence on sex-related differences in rsEEG alpha rhythms recorded in cognitively unimpaired persons (Veldhuizen et al., 1993; Wada et al., 1994; Babiloni et al., 2022).

As novel results, we found that the sex factor also significantly influenced widespread rsEEG alpha source activities estimated in the PDD and DLB patients. Compared to the PDD males, the PDD females displayed lower rsEEG delta source activities and higher rsEEG alpha source activities widely distributed in the cortical regions. The same rsEEG pattern from the sex factor was observed in the DLB patients. The only difference was more marked topographical effects on the rsEEG alpha source activity in the posterior cortical regions. Overall, these results extend to the sex factor previous findings showing altered rsEEG rhythms of quiet vigilance in PDD and DLB patients in relation to matched healthy controls (Walker et al., 2000; Kai et al., 2005; Serizawa et al., 2008; Bonanni et al., 2008; Jackson et al., 2008; Kamei et al., 2010; Pugnetti et al., 2010; Babiloni et al., 2017, 2020b; Pascarelli et al., 2020). They also extend previous findings showing sex-related differences in rsEEG alpha rhythms observed in AD/MCI patients with the present general methodology, namely lower rsEEG alpha source activities estimated in males compared to females (Babiloni et al., 2022). Finally, the novel rsEEG results of the present study complement those of previous neuroimaging investigations. Compared to PDD females, PDD males had more cortical atrophy, thinner cortical thickness, and greater disruption of subcortical white matter connectivity (Yadav et al., 2017; Tremblay et al., 2020; Oltra et al., 2024a). Furthermore, DLB males exhibited more cortical atrophy, particularly in frontal regions, and thinner parietal cortex, occipital cortex, and precuneus thickness compared to DLB females (Abdelnour et al., 2020; Oltra et al., 2024b).

In the interpretation of the present rsEEG results, the lower delta and higher alpha rhythms in the PDD and DLB females over the males cannot be explained by different aging stages or cognitive reserves since the age and education attainment were carefully matched in the statistical data analyses. Instead, the sex-dependent effects on the rsEEG rhythms may be explained by underlying neuroprotective and compensatory neurophysiological mechanisms underlying the vigilance dysregulation. Specifically, the **neuroprotective** mechanisms in the females may be inferred by previous rsEEG evidence showing that the diagnosis of dementia in PDD and DLB patients is typically associated with abnormally high rsEEG delta rhythms and abnormally low rsEEG alpha rhythms (Király et al., 2016). Therefore, the lower rsEEG delta rhythms and higher alpha rhythms in the PDD and DLB females may be due to neuroprotective mechanisms. At the same time, the **compensatory** mechanisms in the PDD and DLB males may be inferred by the consideration that these males had cognitive and motor deficits at the same level as the females, regardless of the worse rsEEG delta and alpha rhythms.

At this early stage of the research, we cannot conclude about the expected complex interplay of genetic, endocrine, socio-cultural, environmental, neuropathological, and neurodegenerative variables influencing the sex-dependent neurophysiological oscillatory mechanisms underpinning the lower rsEEG delta and higher alpha rhythms recorded in the PDD and DLB females compared to the males. Based on the limited data available in the present study, we can only speculate grounding on the potential effects of **sex hormones** on the neurophysiological oscillatory mechanisms described in the **theory of thalamocortical dysrhythmia** (Jeanmonod et al., 1996; Llinás and Steriade, 2006).

The present findings confirm that rsEEG biomarkers, such as those investigated in this study, hold potential utility in clinical practice to improve patient management by considering sex as a critical factor. These biomarkers may also facilitate the selection of the most appropriate diagnostic and therapeutic pathways within the framework of Precision Medicine. Although rsEEG rhythms may not offer highly accurate diagnostic value, they provide valuable insights into the impact of sex-dependent neurodegeneration-related neuropathology on

oscillatory neurophysiological thalamocortical mechanisms. These mechanisms underlie critical functions such as cortical arousal and the regulation of quiet vigilance (Hughes and Crunelli, 2005; Crunelli et al., 2015), which are frequently disrupted in neurodegenerative diseases. Common symptoms associated with these dysfunctions include “mental fog,” daytime drowsiness, and difficulties maintaining adequate vigilance while reading or watching television.

Overall, rsEEG biomarkers are particularly promising due to their noninvasive nature, reproducibility (without learning effects), and applicability across the spectrum from preclinical to dementia stages. Moreover, EEG is a cost-effective technique that relies on recording methods widely available globally, including in lower—and middle-income countries. Notably, a recent multicenter EEG study demonstrated sex-related disparities in the progression of cognitive deficits in aging populations of those countries (Moguilner et al., 2024). This highlights the potential role of rsEEG biomarkers in understanding such a health challenge and in addressing proper public health policies for brain disease prevention in aging, taking into account the sex factor.

A tentative neurophysiological oscillatory model explaining the sex-dependent neuroprotective and compensatory mechanisms in PDD and DLB patients.

According to the theory of thalamocortical dysrhythmia, neurophysiological cortico-basal ganglia, thalamocortical, and re-entrant cortico-thalamic neural circuits would control the brain excitatory-inhibitory balance (arousal) responsible for the vigilance transitions from alertness to sleep (Jeanmonod et al., 1996; Hughes and Crunelli, 2005; Llinás and Steriade, 2006; Crunelli et al., 2015). In healthy brains, that balance would sustain wakefulness during daytime. It would result in the following spatial and frequency features of scalp-recorded rsEEG rhythms: dominant rsEEG alpha (8–12 Hz) rhythms in the posterior areas and negligible delta-theta (< 7 Hz) rhythms (Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020a).

In PDD and DLB patients, rsEEG rhythms recorded in that resting-state (eyes-closed) condition would derange from alpha to delta-theta frequencies, possibly due to an abnormal synchronization at slow frequencies (< 7 Hz) of the activity of cortical pyramidal neurons, triggered by neurons of thalamocortical and corticothalamic circuits showing **bursting** of action potentials at those slow frequencies (Jeanmonod et al., 1996; Llinás and Steriade, 2006). That bursting mode would inhibit information processing in the thalamocortical and cortico-thalamic neurons for the relatively long interval of the membrane hyperpolarization (inhibition) between two bursts of action potentials (Jeanmonod et al., 1996; Llinás and Steriade, 2006). The consequence would be reflected in disorders of vigilance, cognition, and others.

Along the present speculative line, the **neuroprotective** mechanism in the PDD and DLB females may rely on the effects of the hypothalamus-pituitary-**ovaries** axis on the neural circuits described by the theory of thalamocortical dysrhythmia. It is well-known that this axis regulates the level of hypothalamic hormonal releasing factors, pituitary gonadotropin, and (female) ovarian estrogens in the blood (e.g., estradiol). Among estrogens, 17beta estradiol is also synthesized in the female and male brains from cholesterol by aromatase enzymes (Brann et al., 2022). Notably, estrogens might exert a neuroprotective role in brain dopamine pathways of PDD and DLB females by enhancing neural plasticity and mitigating neuroinflammation, cellular oxidative stress, lysosomal dysfunction in autophagy, altered calcium homeostasis, high levels of uric acid and homocysteine, and ischemic and mitochondrial insults (Brann et al., 2022; Raheel et al., 2023). For example, synaptic plasticity within cognitive neural circuits can be promoted by estrogens by modulating the release of brain-derived neurotrophic factor protein levels (Franklin and Perrot-Sinal, 2006).

Preclinical and clinical studies support this speculation. Previous evidence in rodents showed that dopamine release at mesolimbic terminals is greater in females than in males, especially during the peak of the estrogen levels in the ovarian estrous cycle (Zachry et al., 2021). Furthermore, dopamine release is reduced in ovariectomized female

rodents and is recovered by a replacement treatment with estrogens (Zachry et al., 2021). This replacement also mitigated the cognitive deficits induced by lesions in the dopaminergic pathways more effectively than levodopa did (Yadav et al., 2017). In addition, the dopaminergic agonist quinpirole increased the dopamine efflux in basal ganglia more in rodent females than in males (Walker et al., 2006).

Further evidence comes from studies carried out in rodent PD models. In rodent basal ganglia, striatal susceptibility to a dopaminergic neurotoxin was exacerbated by the inhibition of aromatase enzymes involved in the transformation of steroids to estrogens (McArthur et al., 2007; Morale et al., 2008). It was also shown a male-specific vulnerability of rodent dopaminergic nigrostriatal and mesolimbic pathways to neuropathology-neurodegeneration following exposure to neurotoxins associated with PD risk (De Miranda et al., 2019; Adamson et al., 2022). Notably, the cholinergic neuromodulation of those pathways is also dependent on estrogens. Specifically, extranuclear estrogen receptors were found in cholinergic neurons of rodent dorsal striatum, suggesting their modulating role in neural transmission (Almey et al., 2012). Furthermore, the inhibition of the estrogen synthesis prevented the induction of long-term potentiation in rodent striatal cholinergic interneurons, while the replacement of estrogens or the stimulation of dopaminergic receptors recovered it (Tozzi et al., 2015). Finally, an antagonist of cholinergic receptors prevented that recovery due to the stimulation of dopaminergic receptors (Tozzi et al., 2015).

Concerning the clinical studies in PD patients, previous evidence showed the beneficial causal effect of replacement therapy with estradiol over placebo in PD females with vigilance dysregulation reflected by motor fluctuations (Tsang et al., 2000). Other previous evidence in PD females demonstrated a pro-dopaminergic effect of that therapy without dyskinetic side effects (Blanchet et al., 1999). However, mixed results were also reported on the effect of the replacement therapy, so the work is in progress (Dye et al., 2012).

Relating the above data and considerations with the theory of thalamocortical dysrhythmia, it can be speculated that the neuroprotective role of estrogens in PDD and DLB females may be mediated by mitigating pathogenetic neuroinflammation-immunoreactivity and neurotoxic factors affecting synaptic plasticity and the level of neural excitability in the mentioned cortico-basal ganglia, thalamocortical-corticothalamic, and subcortical modulatory (e.g., dopaminergic and cholinergic) neural circuits. The mitigation of these factors may normalize the balance between excitatory and inhibitory neurotransmissions within these circuits involved in the generation of dominant rsEEG alpha rhythms over the aberrant rsEEG delta-theta rhythms in quiet wakefulness.

Along the above speculative line, the **compensatory** mechanisms in the PDD and DLB males, mitigating the cognitive deficits despite deranged rsEEG rhythms, may be grounded on the hypothalamus-pituitary-testicular axis, which regulates testicular testosterone in the blood plasma. Preclinical and clinical studies support this speculation. Previous evidence in rodents showed spatial memory deficits in orchiectomized males, recovered by a replacement treatment with testosterone (Zachry et al., 2021). Furthermore, testosterone mitigated the deleterious effects of hypoxia in rodents due to chronic sleep apneas on behavior and oxidative stress/inflammatory markers from substantia nigra (Snyder et al., 2018). Other evidence comes from studies carried out in rodent PD models. Chronic testosterone administration showed beneficial effects on motor deficits and damage of nigrostriatal and mesolimbic dopaminergic pathways in rodents with a reserpine PD model (Bispo et al., 2022).

Clinical studies showed a reduction in the blood plasma levels of testosterone along with physiological aging and the comparison between age-matched Nold and PD patients (Okun et al., 2002, 2006; Nitkowska et al., 2015). Furthermore, there was a positive correlation between the levels of testosterone in the blood plasma and cognitive performance in Nold persons (LeBlanc et al., 2010) and male PD patients (Okun et al., 2004). A positive correlation was also observed in PD

patients between cognitive performance and an androgenic index based on testosterone and sex hormones binding protein (Nitekowska et al., 2015). However, mixed findings were obtained in PD patients regarding the effects of replacement therapy with testosterone on cognitive status, possibly due to limited sample sizes and relatively short follow-ups of weeks (Okun et al., 2002, 2006). Therefore, the causal effect of that therapy on cognitive functions is still an open issue and should be tested in a future placebo-controlled study with large sample size and follow-ups at 6 and 12 months.

4.1. Methodological remarks

In this exploratory study, clinical and rsEEG datasets were obtained from clinical units that did not undergo a preliminary phase of standardization of operating procedures for data collection in a prospective clinical trial. Additionally, we could only access a relatively small number of PDD and DLB datasets from the present Consortium's archive (www.pdwaves.eu). Considering the exploratory nature of this study, we used a liberal statistical post-hoc test threshold of $p < 0.05$ in some places. Therefore, a future multicentric study should cross-validate the present findings with a larger group of PDD and DLB patients and a more conservative statistical threshold to mitigate the risk of false-positive discoveries with multiple comparisons.

The present study used the 10–10 montage system with 30 scalp electrodes for rsEEG recordings. This electrode montage may be acceptable for exploratory retrospective rsEEG studies in PDD patients using source estimation techniques at low spatial resolution (Babiloni et al., 2020a, 2020b). Due to this limitation, the cortical sources of rsEEG rhythms were estimated in large cortical regions of interest (i.e., cortical lobes) rather than for fine source localization. For this purpose, 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). While eLORETA source estimation using rsEEG recordings from 30 scalp electrodes can yield informative preliminary results, future studies should use high-resolution EEG techniques with 64–256 scalp electrodes to reach a high spatial resolution in the rsEEG source estimation (Liu et al., 2017; Marino et al., 2016).

Lastly, the present rsEEG recordings were obtained only at a single data acquisition session, which precludes a longitudinal evaluation of the sex effects on rsEEG rhythms recorded in PDD and DLB patients. Future studies should consider longitudinal assessments to provide a more comprehensive understanding of these effects over time.

From the clinical point of view, we acknowledge the lack of detailed information on each subject reproductive and hormonal history, such as hormonal age, thus suggesting caution in the interpretation of the observed results.

5. Conclusions

In this exploratory study, we tested the hypothesis that resting-state EEG (rsEEG) delta and alpha sources in patients with Parkinson's Disease Dementia (PDD) and Dementia with Lewy Bodies (DLB) might be influenced by sex. This hypothesis is particularly significant given the higher prevalence of these conditions in males compared to females, suggesting the possibility of sex-dependent neuroprotective or compensatory mechanisms. Indeed, cortical rsEEG rhythms may provide insights into sex-dependent vigilance dysfunctions commonly observed in these patients.

This study revealed significant sex-related differences in the cortical sources of EEG rhythms in patients with PDD and DLB. Specifically, compared to PDD males, PDD females exhibited lower delta and higher alpha source activities across widespread cortical regions from rsEEG data. Similarly, in the DLB group, females displayed lower central-parietal delta and higher posterior alpha source activities. These findings suggest that PDD and DLB males may experience more pronounced

vigilance dysfunctions, such as diurnal drowsiness and sleepiness, compared to their female counterparts, even when cognitive and motor deficits are comparable. It is plausible that sex-related factors, such as hormonal influences and socioeconomic determinants, may contribute to differences in the neurophysiological oscillatory mechanisms underlying cortical arousal and vigilance regulation in PDD and DLB patients.

If these findings are validated in future independent studies, they could have significant implications for both research and clinical practice. Concerning research Implications, future observational studies should explore the role of sex-related hormonal mechanisms in shaping demographic characteristics, brain reserve, and lifestyle-related disease risk factors associated with sex-specific abnormalities in rsEEG rhythms. These abnormalities may reflect differential vulnerabilities to vigilance dysfunctions in PDD and DLB males and females. Additionally, research should focus on elucidating how these factors influence the neurophysiological mechanisms underpinning cortical arousal and vigilance.

For clinical Implications, future clinical trials in PDD and DLB populations aiming to evaluate pharmacological and non-pharmacological interventions for vigilance dysfunctions should incorporate rsEEG abnormalities as neural surrogate biomarkers. Such trials should also account for the potentially greater prevalence and severity of vigilance dysfunctions in males, which may affect sample size calculations and therapy efficacy assessments. Importantly, these trials could investigate whether effective therapies for vigilance dysfunctions can improve not only vigilance regulation but also possibly related core clinical manifestations of PDD and DLB, including visual hallucinations, cognitive fluctuations, and rapid eye movement (REM) sleep behavior disorders, which are closely linked to vigilance regulation.

Abnormalities in rsEEG rhythms may also have practical applications in clinical settings for monitoring and managing vigilance dysfunctions in PDD and DLB patients. These include implementing systematic monitoring strategies, such as home-based telemonitoring of sleep-wake transitions, and tailoring non-invasive brain stimulation therapies to address specific topographic cortical targets of male and female patients.

CRediT authorship contribution statement

Claudio Del Percio: Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roberta Lizio:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Susanna Lopez:** Methodology, Data curation. **Giuseppe Noce:** Methodology, Formal analysis, Data curation. **Dharmendra Jakhar:** Methodology, Data curation. **Matteo Carpi:** Data curation. **Burcu Bölükbaş:** Data curation. **Andrea Soricelli:** Writing – review & editing, Data curation. **Marco Salvatore:** Data curation. **Bahar Güntekin:** Investigation, Data curation. **Görsev Yener:** Investigation, Data curation. **Federico Massa:** Investigation, Data curation. **Dario Arnaldi:** Investigation, Data curation. **Francesco Famà:** Investigation, Data curation. **Matteo Pardini:** Investigation, Data curation. **Raffaele Ferri:** Writing – review & editing, Investigation. **Michele Salerni:** Data curation. **Bartolo Lanuzza:** Data curation. **Fabrizio Stocchi:** Writing – review & editing, Data curation. **Laura Vacca:** Writing – review & editing, Data curation. **Chiara Coletti:** Data curation. **Maira Marizzoni:** Writing – review & editing, Data curation. **John Paul Taylor:** Writing – review & editing, Data curation. **Lutfu Hanoğlu:** Data curation. **Nesrin Helvacı Yılmaz:** Data curation. **İlayda Kıyı:** Data curation. **Yağmur Özbek-İşbitiren:** Data curation. **Giovanni B. Frisoni:** Writing – review & editing, Data curation. **Sofia Cuoco:** Data curation. **Paolo Barone:** Writing – review & editing, Data curation. **Anita D’Anselmo:** Writing – review & editing, Data curation. **Laura Bonanni:** Writing – review & editing, Data curation. **Roberta Biundo:** Data curation. **Fabrizia D’Antonio:** Writing – review & editing, Data curation. **Giuseppe Bruno:** Writing – review & editing, Data curation. **Franco Giubilei:** Writing – review & editing, Data curation. **Francesca De Pandis:**

Writing – review & editing. **Rossella Rotondo:** Writing – review & editing. **Angelo Antonini:** Writing – review & editing, Data curation. **Claudio Babiloni:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

1. None of the authors has any actual or potential 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. No 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.
2. The present study was developed based on the data of the PDWAVES Consortium (www.pdwaves.eu) and the European DLB Consortium (www.e-dlb.com). The Partners and institutional affiliations are reported on the cover page of this manuscript. In this study, the clinical, neuropsychological, and electroencephalographic data collection and analysis in patients with dementia with Lewy bodies and some healthy control participants were partially supported by the funds of “Ricerca Corrente 2022-2023” attributed by the Italian Ministry of Health to the IRCCS Synlab SDN of Naples (Italy), IRCCS Ospedale San Martino of Genoa (Italy), Oasi Research Institute-IRCCS, Troina (Italy), the IRCCS “San Giovanni di Dio” of Brescia, and IRCCS San Raffaele Pisana of Rome (Italy). Furthermore, the clinical, neuropsychological, and electroencephalographic data collection and analysis in patients with Parkinson's disease dementia and other healthy control participants were partially supported by the funds of the “Ricerca Finalizzata 2022-PNRR” project entitled “PREDICT-NEURODEGEN” (Ministry of Health, Grant Agreement: GR-2008-1143091).
3. 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 Disease.
4. All authors have reviewed the contents of the manuscript being submitted, approved of its contents, and validated the accuracy of the data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nbd.2025.106807>.

Data availability

Data will be made available on request.

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