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Resting state EEG rhythms in different stages of chronic kidney disease with mild cognitive impairment

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ABSTRACT

Here, we tested that standard eyes-closed resting-state electroencephalographic (rsEEG) rhythms may characterize patients with mild cognitive impairment due to chronic kidney disease at stages 3–4 (CKDMCI-3&4) in relation to CKDMCI patients under hemodialysis (CKDMCI-H) and mild cognitive impairment (MCI) patients with cerebrovascular disease (CVMCI). Clinical and rsEEG data in 22 CKDMCI-3&4, 15 CKDMCI-H, 18 CVMCI, and 30 matched healthy control (HC) participants were available in a national archive. Spectral rsEEG power density was calculated from delta to gamma frequency bands at scalp electrodes. Results showed that (1) all MCI groups over the HC group showed decreased occipital rsEEG alpha power density; (2) compared to the HC and CVMCI groups, the 2 CKDMCI groups had higher rsEEG delta–theta power density; and (3) the CKDMCI-3&4 group showed the lowest parietal rsEEG alpha power density. The present rsEEG measures may be useful to monitor the impact of circulating uremic toxins on brain regulation of cortical arousal for quiet vigilance in CKDMCI patients.

Abbreviations: rsEEG, resting-state electroencephalographic; MCI, mild cognitive impairment; CKD, chronic kidney disease; CKDMCI-3&4, mild cognitive impairment due to chronic kidney disease at stages 3-4; CKDMCI-H, mild cognitive impairment due to chronic kidney disease in patients under hemodialysis (CKDMCI-H); CVMCI, mild cognitive impairment patients with cerebrovascular disease; HC, healthy control; AD, Alzheimer's disease; ADMCI, patients with mild cognitive impairment due to Alzheimer's disease; MMSE, Mini-Mental State Examination; DETO, Department of Emergency and Organ Transplantation; OPLON, OPportunities for active and healthy LONgevity; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; eLORETA, exact low-resolution brain electromagnetic tomography; TF, transition frequency; IAF, individual alpha frequency; ROI, regions of interest; MANOVA, Multivariate Analysis of Variance; ANOVA, Analysis of Variance; SE, standard error of the mean.

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1. Introduction

Chronic kidney disease (CKD) is defined as abnormal kidney structure or function present for more than 3 months (Levin and Stevens, 2011). It affects 8–16% of the population (Stevens and Levin, 2013; Chen et al., 2019). The loss of kidney function in CKD is progressive and irreversible. Dialysis and kidney transplantation are necessary for patients who progress into end-stage renal disease (Levin and Stevens, 2011).

CKD patients have an increased risk for cerebrovascular disease, with an improving incidence of cardiovascular events with the progression of the loss of kidney function (Go et al., 2008; Spence and Urquhart, 2022). In general, they are characterized by (1) the usual risk factors for cerebrovascular disease; (2) additional risk factors such as volume overload, anemia, oxidative stress, and inflammation; and (3) the cardiovascular complications (Sarnak et al., 2003; Lim et al., 2021). CKD patients have also a high risk of mild cognitive impairment (MCI) and dementia, which may be at least in part induced by cerebrovascular lesions (Lizio et al., 2018; Miglinas et al., 2020).

Spectral measures derived from eyes-closed resting-state electroencephalographic (rsEEG) rhythms were successfully used to assess the neurophysiological correlates in patients with cognitive deficits due to several brain diseases (Babiloni et al., 2006; Franko et al., 2016; Bonanni et al., 2015), even concerning metabolic and renal dysfunctions (Hughes, 1980; Moretti et al., 2007; Lai et al., 2016). As compared to cognitively unimpaired healthy control (HC) seniors, CKD patients were characterized by increased power density in rsEEG delta rhythms (< 4 Hz) in association with renal deficits (Lai et al., 2016; Gadewar et al., 2015; Sagales et al., 1993). Furthermore, CKD patients with severe renal dysfunctions showed high rsEEG delta and delta/alpha (8–12 Hz) power density ratio with more abnormal values in those with greater "frailty" (Chao et al., 2017). Finally, CKD patients also exhibited a power density increase in global rsEEG delta rhythms, inversely correlated with renal functions and cognitive performance measures (Lai et al., 2016).

Notably, a study of our group evaluated the hypothesis that rsEEG cortical sources may disclose differences between groups of patients with MCI due to CKD (CKDMCI) with moderate to severe renal dysfunctions (at stages 3–4; CKDMCI-3&4) and patients with MCI due to Alzheimer's disease (ADMCI; Lizio et al., 2018). It was observed that posterior alpha source activities were more abnormally reduced in the ADMCI than CKDMCI-3&4 group, while widespread delta source activities were abnormally greater in the CKDMCI-3&4 than ADMCI group (Lizio et al., 2018). These results suggest that prodromal AD (neurodegenerative) processes may mainly affect cortical neural synchronization at alpha frequencies underpinning brain arousal and low vigilance in quiet wakefulness. In contrast, CKD (mainly cerebrovascular disease) processes may principally affect cortical neural synchronization at delta frequencies, normally low in healthy people.

Notably, the design of the studies quoted above could not disentangle the impact of uremic (neuro)toxins circulating in the blood and cerebrovascular disease on rsEEG rhythms recorded in CKD patients (Lizio et al., 2018; Lim et al., 2021; Spence and Urquhart, 2022). Indeed, those uremic toxins may accumulate in the brain and have detrimental effects on cerebral resident cells and microcirculation (Natale et al., 2021), possibly inducing MCI and dementia (Peacock, 2020; Kim et al., 2022; Rroji et al., 2022). Such an accumulation can be mitigated by hemodialysis (Lim et al., 2021; Spence and Urquhart, 2022), although it is unable to completely remove the uremic toxins (Meyer et al., 2007) and may induce well-known side effects (e.g., abnormal blood pressure, muscle cramps, itching, sleep problems, anemia, bone diseases).

Here, we tested that standard spectral rsEEG measures may characterize CKDMCI-3&4 patients in relation to CKDMCI patients under hemodialysis (CKDMCI-H) and MCI patients with cerebrovascular disease (CVMCI), possibly unveiling the impact of circulating uremic (neuro)toxins on brain regulation of cortical arousal for quiet vigilance in CKDMCI patients. Clinical and rsEEG data in CKDMCI-3&4, CKDMCI-H, CVMCI, and matched HC participants were available in a national archive. Spectral rsEEG power density was calculated from delta to gamma frequency bands at scalp electrodes. Compared to the datasets used in the reference study by Lizio et al. (2018), the present study was based on original, unpublished datasets in the CKDMCI-H group as a model of CKD with a relatively low level of uremic (neuro) toxins, and in the CVMCI group, as a model of cerebrovascular disease with a relatively normal level of uremic (neuro)toxins.

2. Materials and methods

As mentioned above, all the present clinical and rsEEG datasets relative to the 15 CKDMCI-H and 18 CVMCI patients were original and unpublished. The datasets relative to the 22 CKDMCI-3&4 patients were re-used from the reference study by Lizio et al. (2018). The datasets relative to the 30 HC participants were used in our previous studies as controls for MCI patients.

2.1. Participants

Testing the present study hypothesis was based on the selection of 22 CKDMCI-3&4, 15 CKDMCI-H, 18 CVMCI, and 30 HC datasets from a national archive formed from 60 HC, 35 CVMCI, and 46 CKDMCI participants (Fig. 1).

That selection was obviously made blind on rsEEG data to avoid logical circularity. The criteria for the selection were (1) the maximization of the participants' number in each group; (2) the minimization of the differences in the Mini-Mental State Examination (MMSE) score (Folstein et al., 1975) probing the global cognitive status; and (3) the minimization of the differences of age, sex, and education among the 4 participants' groups among the 3 MCI groups. In the case of the choice of one of two participants with the same demographic features from a given group, it was necessary to minimize the mean demographic differences between that group and the others; the choice was done randomly. More detailed information on the enrolled participants is given in the following.

The CKDMCI patients were serially enrolled in a randomized way at the Department of Emergency and Organ Transplantation of the Hospital of the University of Bari (Italy) during a local clinical trial of the project entitled "*OPportunities for active and healthy LONgevity*" (OPLON - "National Smart Cities" D.D. n. 391/Ric, July 5, 2012; http://www.oplon.eu/it_IT/), granted by Italian Ministry of University and Research. In that clinical trial, 46 CKDMCI participants were recruited. Four out of the 46 CKDMCI patients withdrew from the study. Five of the 46 CKDMCI patients showed artifacts in more than 60% of the rsEEG epochs and were discharged from further analyses. The final groups of CKDMCI patients were formed by 37 CKDMCI patients: 22 CKDMCI-3&4 and 15 CKDMCI-H.

The CVMCI patients were serially enrolled in a randomized way at the IRCCS San Raffaele Pisana and Sapienza University of Rome (Italy) during a local clinical trial of the project entitled "*Does rehabilitation with a 10-Hz sensory stimulation improve brain rhythms and cognitive-motor performance in neurological patients? Towards Internet-based clinical applications at subjects*" (10-Hz rehabilitation; project code: GR-2008-1143090)" granted by the Italian Ministry of Health. In that clinical trial, 35 CVMCI were recruited. Eighteen out of the 35 CVMCI patients were selected to be demographically matched with the 2 CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H).

Finally, the HC participants were enrolled at the following clinical units of our national consortium: IRCCS San Giovanni di Dio Fatebenefratelli of Brescia, IRCCS AOU S Martino-IST of Genoa, and IRCCS Oasi Research Institute of Troina. In those clinical units, 60 HC were recruited. Thirty of the 60 HC patients were selected to be

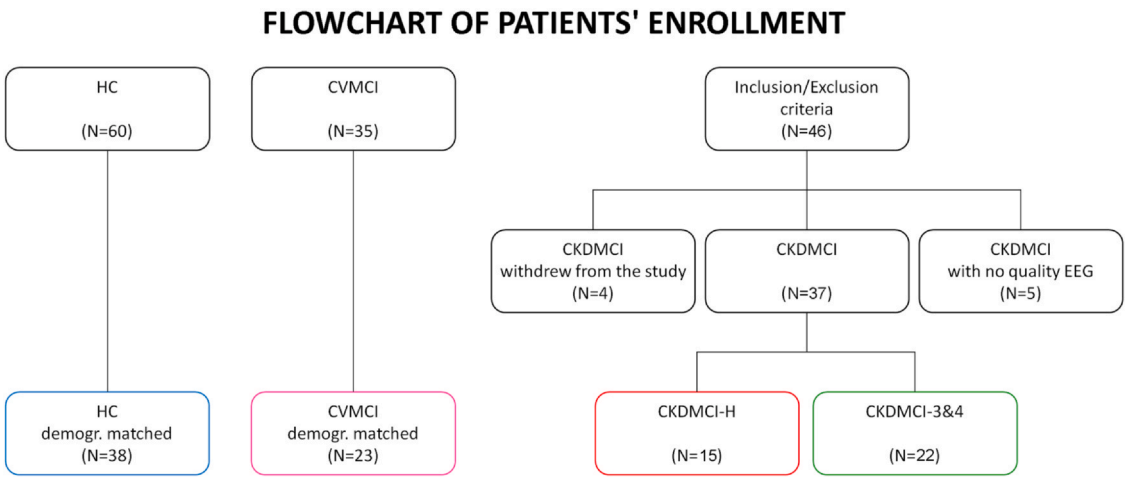

Fig. 1. Flowchart illustrating the selection of 22 patients with mild cognitive impairment due to chronic kidney disease at stages 3–4 (CKDMCI-3&4), 15 patients with MCI due to chronic kidney disease under hemodialysis (CKDMCI-H), 23 patients with MCI due to cerebrovascular disease (CVMCI), and 30 matched healthy control participants (HC). The selection was done in blind on eyes-closed resting-state electroencephalographic (rsEEG) data, considering only the maximization of the enrollment and the minimization of the differences of age, sex, and education among the 4 participants' groups of the present study from the original database formed from 60 HC, 35 CVMCI, and 46 CKDMCI participants.

demographically matched with the 3 MCI groups (i.e., CKDMCI-3&4, CKDMCI-H, and CVMCI).

Fig. 1 illustrates the flowchart of the CKDMCI-3&4, CKDMCI-H, CVMCI, and HC participants' enrollment.

The present investigation was performed in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and received formal approval from the local Ethics Review Board. All participants or their caregivers expressed their written informed consent.

2.2. Diagnostic criteria

In all CKDMCI patients (i.e., CKDMCI-3&4 and CKDMCI-H), the blood sampling was collected and analyzed to extract the levels of glomerular filtration rate, total indoxyl sulphate, total p-cresyl sulphate, blood urea nitrogen, serum calcium, chloremia, serum creatinine, hemoglobin, serum phosphorus, serum potassium, natremia, and uricimia.

All CKDMCI patients were then assessed by physical and neurological exams, the Clinical Dementia Rating (CDR), the Geriatric Depression Scale (GDS; Brown and Schinka, 2005), the modified Hachinski Ischemic Scale (Rosen et al., 1980), the Mini-Mental State Evaluation (MMSE) as a measure of global cognition (Folstein et al., 1975), and the following battery of neuropsychological tests: (1) the Rey-Osterrieth Complex Figure test (immediate and delayed recall) for the executive and visuospatial functions (Osterrieth, 1944); (2) the Prose Memory test (immediate and delayed recall) for the episodic memory (Spinnler and Tognoni, 1987); (3) the Verbal fluency test (both for letters and category) for the language and executive functions (Novelli et al., 1986); and (4) the Trail making test (part A and B) for the visuomotor, attention, and executive functions (Reitan, 1958). The CDR < 1 and the scores of this battery grounded the diagnosis of multi-domain MCI in all CVMCI patients of the present study. Notably, we controlled for important nuisance variables in the data analysis design. All CKDMCI patients were selected to have the GDS (15-item GDS; Brown and Schinka, 2005) score of ≤10, pointing to the **absence of depression**. Furthermore, these CKDMCI patients were selected to have **low cerebrovascular risk** as indicated by modified Hachinski ischemia scores ≤5 (Rosen et al., 1980) and to form groups of hemodialysis vs. conservative pharmacological therapy with **matched MCI status, age, gender, educational attainment, and depression score**.

In all CVMCI patients, clinical, neuropsychological, and rsEEG data were acquired in the sub-acute phase after stroke (about 1 month after the event) when the patient's general condition allowed for the administration of all experimental procedures. All CVMCI patients were assessed by physical and neurological exams, the Stroke Scale of the National Institutes of Health, the CDR, the GDS (Brown and Schinka, 2005), the modified Hachinski Ischemia Scale (Rosen et al., 1980), the MMSE (Folstein et al., 1975), and a standard battery of neuropsychological tests probing short-term and episodic memory, language, executive function/attention, and visuo-construction abilities. The CDR < 1 and the scores of this battery grounded the diagnosis of multi-domain MCI in all CVMCI patients of the present study.

All HC participants of the present study were also assessed by physical and neurological exams, the CDR, the GDS (Brown and Schinka, 2005), the modified Hachinski Ischemia Scale (Rosen et al., 1980), and the MMSE (Folstein et al., 1975). Short-term and episodic memory, language, executive function/attention, and visuo-construction abilities were evaluated during the neurological exam. They all were judged as having a normal cognitive status, and the GDS score showed no depression. Particular attention was devoted to excluding individuals with chronic systemic illnesses (e.g., diabetes mellitus) and any previous or present neurological or psychiatric diseases.

2.3. rsEEG recordings and preliminary data analysis

All participants received rsEEG recordings in the late morning to minimize somnolence. In the CKDMCI-H, the recording was the day between 2 hemodialytic treatments, thus avoiding the acute short-term effects of the hemodialysis (Lai et al., 2018). rsEEG data were acquired for about 5 minutes from a minimum number of 19 exploring scalp electrodes (10–20 System). The linked earlobe reference electrode was preferred, but not mandatory, to respect the clinical recording units' methodological facilities and standard internal protocols. A ground electrode was typically located between the AFz and Fz electrodes, and electrode impedances were kept below 5 KOhm. Horizontal and vertical electro-oculographic activities (0.3–70 Hz bandpass) were also recorded to evaluate blinking and eye movements.

Band-passing (0.1 Hz and 100 Hz, to avoid aliasing) and down-sampling to 128 Hz (when recorded with higher sampling frequency) were applied to the recorded rsEEG data. rsEEG recording was partitioned into 2-second consecutive epochs and analyzed offline. Particular attention was paid to the removal of epochs affected by physiological (i.e., ocular/ blinking, muscular, and head movements) or non-physiological (i.e., sweat, bad contact between electrodes and scalp, etc.) artifacts based on the visual analysis by two experts of EEG signals (C.D.P., R.L., G.N., or S.L.).

2.4. Scalp power density of rsEEG rhythms

The power density of scalp rsEEG rhythms (0.5 Hz resolution) at each electrode was computed on artifacts-free rsEEG epochs with a standard digital FFT-based analysis (Welch technique, Hanning windowing function, no phase shift), using the official freeware tool called exact low-resolution brain electromagnetic tomography (Pascual-Marqui, 2007).

The EEG frequency bands of interest were individually identified based on the transition frequency (TF) and individual alpha frequency (IAF) landmarks (Klimesch, 1999; 2012). The TF marks the transition frequency between the theta and alpha bands, defined as the minimum rsEEG power density between 3 and 8 Hz. The IAF is defined as the maximum power density peak between 6 and 14 Hz. Based on the TF and IAF, we estimated the individual delta, theta, and alpha bands as follows: delta from TF −4 Hz to TF −2 Hz, theta from TF −2 Hz to TF, alpha 1 from TF to the frequency midpoint of the TF–IAF range and alpha 2 from that midpoint to IAF, and alpha 3 (high-frequency alpha) from IAF to IAF +2 Hz. Then, we considered the predetermined beta 1 (14–20 Hz), beta 2 (20–30 Hz), and gamma (30–40 Hz) bands.

For each participant, the regional normalized rsEEG power density at the scalp electrode level was evaluated. In detail, the procedure was performed as follows: (1) for each participant, the scalp rsEEG power density at each electrode was normalized to the mean of the power density values across all frequency bins (i.e., 0.5–45 Hz) and electrodes (i.e., 19); (2) the regional normalized scalp rsEEG power density was calculated averaging the normalized scalp rsEEG power density within the following groups of electrodes (regions of interest, ROIs): F7, F3, Fz, F4 and F8 for the frontal, C3, Cz, and C4 for the central, P3, Pz, and P4 for the parietal, T3, T4, T5, and T6 for the temporal, and O1 and O2 for the occipital regions; and (3) the regional normalized scalp rsEEG power density values within each band of interest were averaged to obtain the frequency band values.

2.5. Statistical analysis of the regional normalized scalp rsEEG power density

A statistical session was performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test the working hypothesis that resting-state eyes-closed rsEEG rhythms at delta, theta, and alpha frequencies may differ among CKDMCI-3&4, CKDMCI-H, CVMCI, and HC groups. To address that issue, a multivariate analysis of variance (MANOVA) was computed ($p < 0.05$). The MANOVA used the regional normalized scalp rsEEG power density values as multiple dependent variables. Since MANOVA implies that dependent variables approximate Gaussian distributions and the regional normalized scalp rsEEG power density distributions may not fit this feature, we computed the Log10 transformation of rsEEG power density values for each participant and frequency band of interest. Afterward, we confirmed their Gaussian distribution by the Kolmogorov–Smirnov test ($p < 0.05$).

Mauchly's test evaluated the sphericity assumption. The Greenhouse-Geisser procedure was used to adjust for lack of sphericity (i.e., the correction functions as both an estimate of epsilon and a correction for lack of sphericity). Duncan test was used for post-hoc comparisons ($p < 0.05$, corrected for multiple comparisons).

The MANOVA factors were Group (HC, CVMCI, CKDMCI-3&4, and CKDMCI-H), band (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, gamma), and ROI (frontal, central, parietal, occipital, and temporal). The confirmation of the working hypothesis would require (1) a statistically significant ANOVA interaction including the factors group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$ Bonferroni corrected) differences in the regional/global normalized scalp rsEEG power density at delta, theta, and alpha frequencies among the three MCI groups ($p < 0.05$ Bonferroni corrected).

The statistical analysis results were controlled by the iterative (leave-one-out) Grubbs' test detecting the presence of one or more outliers in the distribution of the regional normalized scalp rsEEG power density values. We tested the null hypothesis of the non-outlier status at the arbitrary threshold of $p > 0.001$ to remove only individual values with a high probability of being outliers.

3. Results

3.1. Demographic data and global cognitive status in the HC, CVMCI, CKDMCI-3&4, and CKDMCI-H groups

Table 1 summarizes (1) the most relevant demographic (i.e., age, sex, and education attainment) and clinical (i.e., MMSE score) features observed in the HC, CVMCI, CKDMCI-3&4, and CKDMCI-H groups and (2) the presence or absence of statistically significant differences ($p < 0.05$) between the 4 groups for the age (ANOVA), sex (Freeman–Halton test), educational attainment (ANOVA), and MMSE score (Kruskal–Wallis ANOVA). As expected, a statistically significant difference was found for the MMSE score ($H = 34.3$, $p < 0.001$), showing a higher score in the HC group than the three MCI groups (i.e., CVMCI, CKDMCI-3&4, and CKDMCI-H). On the contrary, no statistically significant differences were found for the age, sex, and educational attainment among the 4 groups ($p > 0.05$).

Table 1
Mean values (± SE) of the demographic characteristics and global cognitive status (i.e., MMSE score) as well as the results of their statistical comparisons ($p < 0.05$) in the groups of HC participants, CVMCI, CKDMCI-3&4, and CKDMCI-H

	HC	CVMCI	CKDMCI-3&4	CKDMCI-H	Statistical analysis
N	30	18	22	15	
Age (± SE)	69.7 (± 1.2)	71.3 (± 1.8)	72.3 (± 1.1)	71.3 (± 1.7)	ANOVA: n.s.
Sex (M/F)	17/13	10/8	15/7	10/5	Freeman–Halton: n.s.
Education (± SE)	11.0 (± 0.8)	10.7 (± 0.7)	12.3 (± 1.5)	12.3 (± 2.0)	ANOVA: n.s.
MMSE (± SE)	28.6 (± 0.2)	25.1 (± 0.6)	25.2 (± 0.6)	26.1 (± 0.6)	Kruskal–Wallis ANOVA: $H = 34.34$ $p < 0.001$

Key: CKDMCI-3&4, patients with MCI due to chronic kidney disease at pathological stages 3–4; CKDMCI-H, patients with MCI due chronic kidney disease under hemodialysis; CVMCI, patients with mild cognitive impairment due to cerebrovascular disease; HC, healthy control; MMSE, Mini-Mental State Examination; n.s., not significant, SE, standard error of the mean.

Table 2
Mean values (± SE) of the neuropsychological tests and results of their statistical comparisons ($p < 0.05$, Bonferroni corrected) in the CKDMCI-3&4 and CKDMCI-H groups (for each neuropsychological test, the cut-point for normality and the percentage of the CKDMCI patients with the pathological score are also reported)

Neuropsychological data				
	CKDMCI-3&4 Mean ± SE (%participants with abnormal score)	CKDMCI-H Mean ± SE (%participants with abnormal score)	T test	Cut point for normality
Prose memory test, immediate recall	5.5 ± 0.4 (100%)	5.1 ± 0.6 (100%)	n.s.	> 8
Prose memory test, delayed recall	5.3 ± 0.6 (100%)	5.4 ± 0.6 (100%)	n.s.	> 8
Rey figure, copy	31.5 ± 1.4 (26%)	30.8 ± 1.5 (33%)	n.s.	> 28.8
Rey figure, delayed recall	16.8 ± 1.5 (12%)	19.9 ± 1.2 (0%)	n.s.	> 9.47
Trail making test A	60.9 ± 6.7 (14%)	69.6 ± 11.2 (20%)	n.s.	< 93
Trail making test B	120.5 ± 13.5 (5%)	154.4 ± 21.6 (7%)	n.s.	< 282
Trail making test B-A	59.7 ± 9.5 (5%)	84.8 ± 11.1 (7%)	n.s.	< 186
Verbal fluency for letter	33.4 ± 2.0 (0%)	29.1 ± 1.6 (0%)	n.s.	> 17
Verbal fluency for category	37.1 ± 1.7 (0%)	35.3 ± 1.8 (0%)	n.s.	> 25

Key: CVMCI, patients with mild cognitive impairment due cerebrovascular disease; CKDMCI-3&4, patients with mild cognitive impairment due to chronic kidney disease at stages 3–4; CKDMCI-H, patients with mild cognitive impairment due to chronic kidney disease under hemodialysis; n.s., not significant; SE, standard error of the mean.

3.2. Neuropsychological data in the CKDMCI-3&4 and CKDMCI-H groups

Table 2 reports (1) the mean values (± standard error of the mean, SE) of the neuropsychological tests (i.e., Prose memory test immediate and delayed recall, Rey figure immediate and delayed recall, Trail making test A, B, B–A, Verbal fluency for letters and categories) in the 2 CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H); (2) the cut-off scores of the above-mentioned neuropsychological tests; (3) the percentage of the CKDMCI participants with the pathological score for each group; and (4) the presence or absence of statistically significant differences (T-test, $p < 0.05$ Bonferroni corrected) between the 2 CKDMCI groups for the neuropsychological tests used. To consider the inflating effects of repetitive univariate tests, the statistical threshold was set at $p < 0.00556$ (i.e., 9 neuropsychological tests, $p < 0.05/9 = 0.00556$) to obtain the Bonferroni correction at $p < 0.05$. No statistically significant differences were found, either with ($p > 0.00556$) or without ($p > 0.05$) correction.

3.3. Clinical and biological data in the CKDMCI-3&4 and CKDMCI-H groups

Table 3 reports (1) the mean values (± SE) of the clinical data (i.e., Clinical Dementia Rating, Hachinski Ischemic Scale, and Geriatric Depression Scale) and biological markers (i.e., glomerular filtration rate, total indoxyl sulphate, total p-cresyl sulphate, blood urea nitrogen, serum calcium, chloremia, serum creatinine, hemoglobin, serum phosphorus, serum potassium, natremia, and uricimia) in the 2 CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H); (2) the cut-off scores of those mentioned above clinical and biological markers; (3) the percentage of the CKDMCI participants with the pathological score for each group; and (4) the presence or absence of statistically significant differences (T-test, $p < 0.05$ Bonferroni corrected) between the 2 CKDMCI groups for the clinical and biological markers used. To consider the inflating effects of repetitive univariate tests, the statistical threshold was set at $p < 0.003$ (i.e., 15 clinical and biological tests, $p < 0.05/15 = 0.003$) to obtain the Bonferroni correction at $p < 0.05$. No statistically significant differences were found for clinical markers, either with ($p > 0.003$) or without ($p > 0.05$) correction. On the contrary, as expected, statistically significant differences ($p < 0.003$) were found for the following biological markers: glomerular filtration rate, blood urea nitrogen, serum creatinine, hemoglobin, serum phosphorus, serum potassium, and uricemia.

3.4. Regional normalized scalp rsEEG power density in the HC, CVMCI, CKDMCI-3&4 and CKDMCI-H groups

The mean TF was 5.9 Hz (± 0.2 SE) in the HC group, 5.7 Hz (± 0.2 SE) in the CVMCI group, 5.8 Hz (± 0.3 SE) in the CKDMCI-3&4 group, and 5.1 Hz (± 0.2 SE) in the CKDMCI-H group. Furthermore, the mean IAFp was 9.4 Hz (± 0.2 SE) in the HC group, 9.1 Hz (± 0.2 SE) in the CVMCI group, 9.3 Hz (± 0.3 SE) in the CKDMCI-3&4 group, and 9.0 Hz (± 0.3 SE) in the CKDMCI-H group. Two ANOVAs ($p < 0.05$) were performed to evaluate the presence or absence of statistically significant differences ($p < 0.05$) among the 4 groups (i.e., HC, CVMCI, CKDMCI-3&4, and CKDMCI-H). No statistically significant differences were found ($p > 0.05$).

Fig. 2 shows the mean values (± SE, log-10 transformed) of the regional normalized scalp rsEEG power density relative to a statistically significant MANOVA interaction effect ($F = 3.9$, $p < 0.001$) among the factors group (HC, CVMCI, CKDMCI-3&4, and CKDMCI-H), band (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, gamma), and ROI (frontal, central, parietal, occipital, and temporal). The HC group showed maximum magnitude in the occipital (maximum), parietal, and temporal, alpha 2–3 power density. Compared to the HC group, the 3 MCI groups (i.e., CVMCI, CKDMCI-3&4, and CKDMCI-H) showed a substantial decrease in the occipital alpha 2–3 power density. Compared to the HC and CVMCI groups, the 2 CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H) showed a substantial increase in the frontal, central, and parietal delta–theta power density. Finally, to the HC, CVMCI, and CKDMCI-H groups, the CKDMCI-3&4 group showed a clear decrease in the parietal alpha 2–3 power density. Table 4 reports the Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 8 frequency bands × 5 ROI = 40, $p < 0.05/40 = 0.00125$), size effect by Cohen's d, and sample size by an alpha level of 0.05 and desired power of 0.8 for the above MANOVA group × band × ROI interaction.

The MANOVA also showed a statistically significant group × band interaction effect ($F = 5.2$, $p < 0.001$; see Supplementary Materials).

Of note, these findings were not due to outliers from regional normalized scalp rsEEG power densities (log-10 transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

3.5. Control analysis

In the Supplementary Materials, we reported the results of a control analysis corroborating the main analysis results. That control analysis showed that occipital alpha 2–3 normalized scalp rsEEG power density was related to MMSE score as an index of global cognition.

Table 3
Mean values (± SE) of the clinical and biological data and results of their statistical comparisons ($p < 0.05$, Bonferroni corrected) in the CKDMCI-3&4 and CKDMCI-H groups (for each clinical and biological data, the cut-point for normality and the percentage of the CKDMCI patients with the pathological score are also reported)

Clinical and biological data				
	CKDMCI-3&4 Mean ± SE (%participants with abnormal score)	CKDMCI-H Mean ± SE (%participants with abnormal score)	T test	Cut point for normality
Clinical Dementia Rating (CDR)	0.3 ± 0.1 SE (60%)	0.3 ± 0.1 SE (40%)	n.s.	0 dementia absent
Hachinski Ischemic Scale (HIS)	1.2 ± 0.1 SE (100%)	1.6 ± 0.4 SE (100%)	n.s.	0 ischemia symptom absent
Geriatric Depression Scale (GDS)	3.0 ± 0.4 SE (0%)	3.7 ± 0.5 SE (0%)	n.s.	≤10 depression absent
Glomerular Filtration Rate (eGFR; ml/min)	39.9 ± 2.6 SE (100% - N = 22)	5.9 ± 0.5 SE (100% - N = 15)	$p < 0.001$	> 90 ml/min
Total indoxyl sulphate (μg/ml)	3.9 ± 1.7 SE (0% - N = 9)	12.2 ± 4.5 SE (0% - N = 4)	$p < 0.05$	< 0.76 mg/100 ml
Total p-cresyl sulphate (μg/ml)	12.0 ± 2.8 SE (0%)	21.8 ± 7.4 SE (0%)	n.s.	< 0.051 mg/100 ml
Serum calcium (mg/dl)	9.1 ± 0.2 SE (13.3%)	10.0 ± 0.3 SE (55.6%)	n.s.	8.5–10.5 mg/dl
Blood urea nitrogen (mg/dl)	2.4 ± 0.2 SE (100%)	0.6 ± 0.1 SE (100%)	$p < 0.001$	6–20 mg/dl
Chloremia (mEq/l)	101.5 ± 1.4 SE (33.3%)	102.6 ± 0.6 SE (0%)	n.s.	98–107 mEq/l
Serum creatinine (mg/dl)	1.7 ± 0.1 SE (70%)	5.1 ± 1.3 SE (100%)	$p < 0.001$	0.7–1.3 mg/dl
Hemoglobin (gr/dl)	13.3 ± 0.4 SE (41%)	11.1 ± 0.4 SE (87%)	$p < 0.005$	12.4–14.9 g/dl (male) 11.7–13.8 g/dl (female)
Serum phosphorus (mg/dl)	3.5 ± 0.3 SE (20%)	1.8 ± 0.2 SE (66%)	$p < 0.001$	2.50–4.80 mg/dl
Serum potassium (mEq/l)	4.7 ± 0.1 SE (21.1%)	3.7 ± 0.1 SE (22.2%)	$p < 0.001$	3.5–5 mEq/l
Natremia (mEq/l)	140.5 ± 0.7 SE (15.8%)	137.8 ± 0.9 SE (22.2%)	$p < 0.01$	136–145 mEq/l
Uricemia (mg/dl)	5.1 ± 0.4 SE (13.3%)	1.2 ± 0.1 SE (100%)	$p < 0.001$	3.4–7.0 mg/dl (male) 2.4–5.7 mg/dl (female)

Key: CVMCI, patients with mild cognitive impairment due cerebrovascular disease; CKDMCI-3&4, patients with mild cognitive impairment due to chronic kidney disease at stages 3–4; CKDMCI-H, patients with mild cognitive impairment due to chronic kidney disease under hemodialysis; n.s., not significant; SE, standard error of the mean.

4. Discussion

The present retrospective and cross-sectional investigation can be considered a new significant experimental step forward in relation to the reference study by Lizio et al. (2018). From a clinical point of view, a significant novelty is represented by the inclusion of two new groups of patients: a group of CKDMCI patients on hemodialysis and a group of CVMCI patients. These groups allowed us to test the hypothesis that spectral rsEEG measures may show different abnormalities in CKDMCI patients due to different disease stages and treatments regardless of the cerebrovascular disease. Of note, the experimental design included the CKDMCI-3&4 group as a model of cerebrovascular disease with a high level of uremic (neuro)toxins, the CKDMCI-H group as a model of cerebrovascular disease with a low/medium level of uremic toxins, and the CVMCI group as a model of cerebrovascular disease without an abnormal level of uremic toxins. We hypothesized that due to the high level of circulating uremic toxins, the group of CKDMCI-3&4 patients might be characterized by higher abnormalities in spectral rsEEG measures compared to the groups of CKDMCI-H and CVMCI patients.

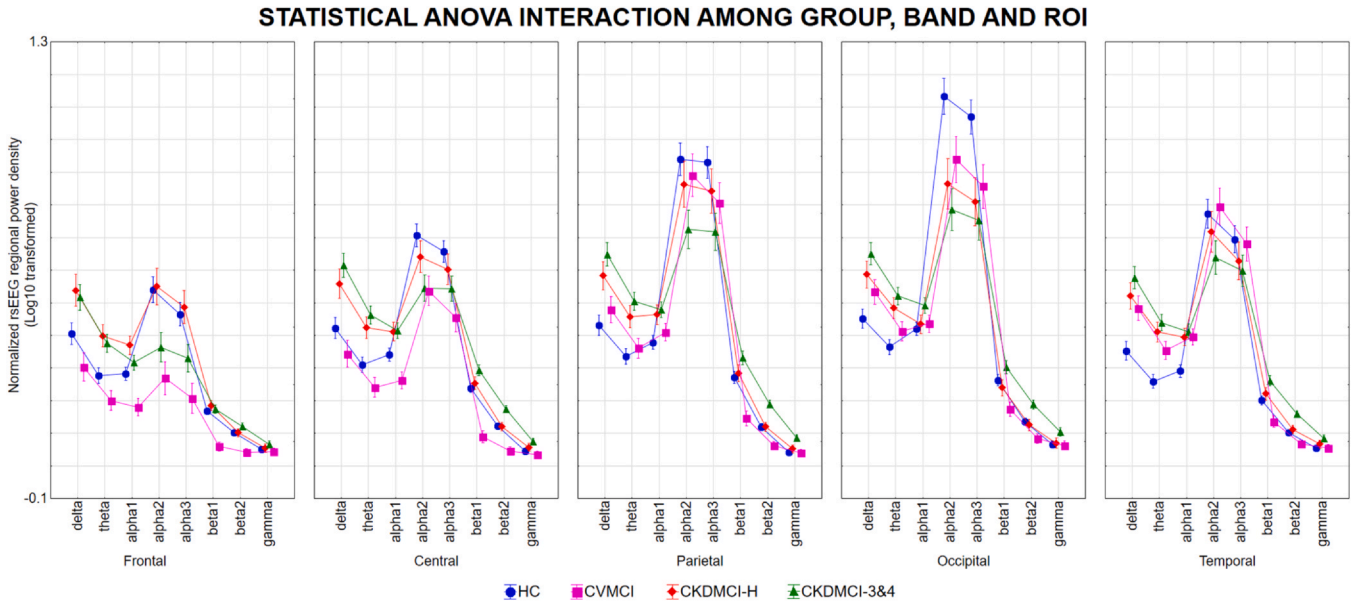

Fig. 2. Regional normalized scalp rsEEG power density (mean across participants, log-10 transformed) relative to a statistical MANOVA interaction ($F = 3.9$, $p < 0.001$) among the group (HC, CVMCI, CKDMCI-3&4, and CKDMCI-H), band (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, gamma), and ROI (frontal, central, parietal, occipital, and temporal). Abbreviations: CKDMCI-3&4, patients with mild cognitive impairment due to chronic kidney disease at stages 3–4; CKDMCI-H, patients with mild cognitive impairment due to chronic kidney disease under hemodialysis; CVMCI, patients with mild cognitive impairment due cerebrovascular disease; HC, healthy control participants; MANOVA, multivariate analysis of variance; ROI, region of interest; rsEEG, resting-state electroencephalographic.

Table 4
Duncan planned post-hoc ($p < 0.05$ Bonferroni correction for 8 frequency bands × 5 ROI = 40, $p < 0.05/40 = 0.00125$), size effect by Cohen's d, and sample size by an alpha level of 0.05 and desired power of 0.8 for a statistically significant MANOVA interaction effect ($F = 3.9$, $p < 0.001$) among the factors group (HC, CVMCI, CKDMCI-3&4, and CKDMCI-H) and band (delta, theta, alpha1, alpha2, alpha3, beta1, beta2, gamma), and region of interest (ROI; frontal, central, parietal, occipital, and temporal)

Duncan post-hoc comparisons, Cohen's D and sample size							
		HC vs. CVMCI	HC vs. CKDMCI-H	HC vs. CKDMCI-3&4	CVMCI vs. CKDMCI-H	CVMCI vs. CKDMCI-3&4	CKDMCI-H vs. CKDMCI-3&4
Delta	F	-	$p < 0.001$ −0.83 (24)	-	$p < 0.001$ −1.18 (13)	$p < 0.001$ −1.06 (16)	-
	C	-	$p < 0.001$ −0.90 (21)	$p < 0.001$ −1.15 (13)	$p < 0.001$ −1.21 (12)	$p < 0.001$ −1.42 (9)	-
	P	-	$p < 0.001$ −1.12 (14)	$p < 0.001$ −1.41 (10)	-	$p < 0.001$ −0.89 (21)	-
	O	-	$p < 0.001$ −1.13 (14)	$p < 0.001$ −1.44 (9)	-	-	-
	T	$p < 0.001$ -0.91 (21)	$p < 0.001$ −1.34 (10)	$p < 0.001$ −1.64 (7)	-	-	-
Theta	F	-	$p < 0.001$ −1.05 (16)	-	$p < 0.001$ −1.39 (10)	$p < 0.001$ −1.27 (11)	-
	C	-	-	$p < 0.001$ −1.20 (13)	$p < 0.001$ −1.47 (9)	$p < 0.001$ −1.66 (7)	-
	P	-	$p < 0.001$ −1.02 (17)	$p < 0.001$ −1.35 (10)	-	$p < 0.001$ −1.07 (15)	-
	O	-	$p < 0.001$ −1.05 (16)	$p < 0.001$ −1.38 (10)	-	-	-
	T	-	$p < 0.001$ −1.50 (9)	$p < 0.001$ −1.78 (7)	-	-	-
Alpha1	F	-	-	-	$p < 0.001$ −1.57 (8)	$p < 0.001$ −1.33 (10)	-
	C	-	-	-	$p < 0.0001$ −1.33 (10)	$p < 0.0001$ −1.53 (8)	-
	P	-	-	-	-	-	-
	O	-	-	-	-	-	-
	T	-	-	$p < 0.001$ −1.87 (6)	-	-	-
Alpha2	F	$p < 0.001$ 1.18 (13)	-	$p < 0.001$ 0.85 (23)	$p < 0.001$ −1.31 (11)	-	$p < 0.001$ 1.03 (16)
	C	$p < 0.001$ 0.80 (26)	-	$p < 0.001$ 0.97 (18)	-	-	-
	P	-	-	$p < 0.001$ 0.95 (19)	-	$p < 0.001$ 0.54 (55)	$p < 0.001$ 0.67 (37)
	O	$p < 0.001$ 0.61 (44)	$p < 0.001$ 1.04 (16)	$p < 0.001$ 1.37 (10)	-	$p < 0.001$ 0.47 (73)	-
	T	-	-	$p < 0.005$ 0.66 (38)	-	$p < 0.001$ 0.57 (50)	-
Alpha3	F	$p < 0.001$ 1.36 (10)	-	$p < 0.001$ 0.74 (30)	$p < 0.001$ −1.39 (10)	$p < 0.005$ −0.96 (19)	$p < 0.001$ 0.82 (25)
	C	$p < 0.001$ 1.05 (16)	-	$p < 0.005$ 0.70 (34)	$p < 0.001$ −0.73 (31)	-	-
	P	-	-	$p < 0.001$ 0.93 (20)	-	$p < 0.001$ 0.60 (50)	$p < 0.001$ 0.61 (44)
	O	$p < 0.001$ 0.70 (34)	$p < 0.001$ 0.99 (18)	$p < 0.001$ 1.20 (13)	-	-	-
	T	-	-	-	-	-	-

Key: CVMCI, patients with mild cognitive impairment due cerebrovascular disease; CKDMCI-3&4, patients with mild cognitive impairment due to chronic kidney disease at stages 3–4; CKDMCI-H, patients with mild cognitive impairment due to chronic kidney disease under hemodialysis, HC, healthy control participants.

The present original results can be summarized as follows: (1) compared to the HC group, the three MCI groups (i.e., CVMCI, CKDMCI-3&4, and CKDMCI-H) showed a substantial decrease in the occipital rsEEG alpha power density; (2) compared to the HC and CVMCI groups, the two CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H) showed a substantial increase in the frontal, central, and parietal rsEEG delta–theta power density; and (3) compared to the HC, CVMCI, and CKDMCI-H groups, the CKDMCI-3&4 group showed a clear decrease in the parietal rsEEG alpha power density. They extend and complement the following previous rsEEG studies showing that: (1) cortical rsEEG delta rhythms were more abnormal in the present CKDMCI patients at the disease stages 3–4 than in ADMCI patients (Lizio et al., 2018); (2) depression levels, cognitive deficits, and global rsEEG delta rhythms averaged across all scalp sensors were significantly greater in magnitude in CKD patients on hemodialysis than those under conservative pharmacological treatments (Lai et al., 2016); and (3) topographically widespread rsEEG delta rhythms were significantly greater in magnitude in CKD hemodialysis patients with low-moderate clinical "frailty" as compared to those with higher clinical "frailty" (Chao et al., 2017).

When compared to the HC group, both CKDMCI groups of the present study showed higher frontal-centro-parietal rsEEG delta–theta rhythms, possibly due to abnormalities in cortico-thalamic and thalamocortical functional connectivity involved in cortical neural synchronization mechanisms underpinning cortical arousal in relation to vigilance and sleep-wake cycle (Steriade and Llinás, 1988; Dossi et al., 1992; Pfurtscheller and Lopes da Silva, 1999; Rodriguez et al., 2016; Latreille et al., 2016). Both CKDMCI groups also showed reduced occipital rsEEG alpha rhythms, possibly due to abnormalities in ascending subcortical cholinergic neuromodulator systems impinging upon cortico-thalamic and thalamocortical functional connectivity involved in the mentioned cortical neural synchronization mechanisms (Babiloni et al., 2020a, 2020b; Crunelli et al., 2015; Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999).

It is presently unclear why those rsEEG delta–theta and alpha rhythms were so abnormal in the CKDMCI patients under conventional therapy and on hemodialysis, with a particular abnormality in the posterior rsEEG alpha rhythms in the CKDMCI patients on hemodialysis. According to a general theoretical framework, the mentioned abnormalities at centro-parietal rsEEG delta–theta and alpha rhythms in CKDMCI patients may reflect the effects of an abnormal accumulation of neurotoxic proteins, chronic neuroinflammation, cerebrovascular disorders, and neurodegeneration on the neurophysiological oscillatory mechanisms shortly described above (Babiloni et al., 2013a, 2013b; Killiany et al., 1993; Fernandez et al., 2003; Peraza et al., 2014, 2015; Jovicich et al., 2019; Rodriguez et al., 2016; Latreille et al., 2016). Furthermore, it can be speculated that in the present CKDMCI patients, circulating neurotoxic proteins in the blood may induce oxidative stress, uremia, and neuroinflammation with a significant role in the alteration in rsEEG rhythms reflecting those abnormal neurophysiological mechanisms, in addition to cerebrovascular lesions typically observed in the patients' cerebral white matter (Berr et al., 2000; Ikizler et al., 2002; Himmelfarb, 2009; Seliger and Longstreth, 2008; Wardlaw et al., 2003; Kalimo, 2003; Weiner et al., 2009; De Deyn et al., 2009; Bugnicourt et al., 2013).

In the interpretation of the present findings, the following methodological limitations should be carefully considered: (1) the relatively small number of CKDMCI patients (i.e., N = 15–22); (2) the different calendar time, settings, and equipment used in the rsEEG recordings for the CDKMCI, CVMCI, and HC participants; (3) the lack of clinical follow-ups in the MCI patients; and (4) lack of neuroimaging scans and relevant fluid biomarkers. These limitations suggest the need for a future prospective, longitudinal, cross-validation, and multi-center study in which clinical, neuropsychological, biofluid, rsEEG, and neuroimaging data will be collected in harmonized ways and centrally analyzed at baseline and follow-ups in new cohorts of CDKMCI, CVMCI, and HC participants in the framework of the same clinical trial.

5. Conclusions

This retrospective and exploratory study tested the hypothesis that rsEEG rhythms may characterize CKDMCI patients in relation to (1) different disease stages and treatment and (2) patients with CVMCI.

The original results of the present study showed that compared to the HC group, the three MCI groups (i.e., CVMCI, CKDMCI-3&4, and CKDMCI-H) showed a substantial decrease in the occipital rsEEG alpha power density. Compared to the HC and CVMCI groups, the two CKDMCI groups (i.e., CKDMCI-3&4 and CKDMCI-H) showed a substantial increase in the frontal, central, and parietal rsEEG delta–theta power density. Finally, compared to the HC, CVMCI, and CKDMCI-H groups, the CKDMCI-3&4 group showed the lowest parietal rsEEG alpha power density.

The present standard spectral rsEEG measures grounded on the delta, theta, and alpha rhythms did unveil different topographical abnormalities in CKDMCI patients evaluated at different disease stages and treatments, partially independent of cerebrovascular lesions. These results suggest that beyond the cerebrovascular impairment, circulating uremic toxins (especially expressed in the present CKDMCI-3&4) may have a peculiar deleterious effect on brain neurophysiological oscillatory mechanisms regulating cortical arousal and vigilance. Therefore, the use of hemodialytic treatment in CKDMCI-3&4 patients should be carefully considered to improve the regulation of cortical arousal and vigilance, impacting their quality of social life, for example, to allow following quiet TV programs and social conversions with friends and relatives. In this sense, the present rsEEG measures may be useful topographical biomarkers to monitor that brain function in those CKDMCI patients and the effects of pharmacological and non-pharmacological interventions.

Disclosure statement

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

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The present study was mainly based on data collected in patients with chronic kidney disease at the Department of Emergency and Organ Transplantation of the Policlinico of Bari, Italy, in the framework of the project with the short title "OPLON" (OPportunities for active and healthy LONgevity; "National Smart Cities" D.D. n. 391/Ric, July 5, 2012), granted by the Italian Ministry of University and Research.

All patients with cerebrovascular lesions were based on data collected at the IRCCS San Raffaele Pisana and Sapienza University of Rome (Italy) in the project entitled "Does rehabilitation with a 10-Hz sensory stimulation improve brain rhythms and cognitive-motor performance in neurological patients? Towards Internet-based clinical applications at participants" (10-Hz rehabilitation; project code: GR-2008–1143090)", granted by the Italian Ministry of Health.

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CRediT authorship contribution statement

Roberta Lizio, Claudio Babiloni, Claudio Del Percio: ***Conceptualization, Methodology, Formal analysis, Validation, Writing - Original Draft, Supervision, Writing - Review & Editing, Project administration.*** Susanna Lopez: ***Conceptualization, Methodology, Formal analysis, Writing - Original Draft.*** Giuseppe Noce: ***Formal analysis, Writing - Review & Editing.*** Antonia Losurdo, Lucia Vernò, Marina De Tommaso, Anna Montemurno, Giuseppe Dalfino, Pietro Cirillo, Andrea Soricelli, Raffaele Ferri, Valentina Catania, Flavio Nobili, Franco Giubilei, Carla Buttinelli, Giovanni B. Frisoni, Fabrizio Stocchi, Anna Maria Scisci, Nicola Mastrofilippo, Deni Aldo Procaccini, and Loreto Gesualdo: ***Investigation, Data Curation, Project administration, Writing - Review & Editing.***

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.05.014.

References

Babiloni, C., Benussi, L., Binetti, G., Bosco, P., Busonero, G., Cesaretti, S., Dal Forno, G., Del Percio, C., Ferri, R., Frisoni, G., Ghidoni, R., Rodriguez, G., Squitti, R., Rossini, P.M., 2006. Genotype (cystatin C) and EEG phenotype in Alzheimer disease and mild cognitive impairment: a multicentric study. Neuroimage 29 (3), 948–964. https://doi.org/10.1016/j.neuroimage.2005.08.030

Babiloni, C., Infarinato, F., Triggiani, A.I., Lizio, R., Percio, C.Del, Marzano, N., Richardson, J.C., 2013a. Resting state EEG rhythms as network disease markers for drug discovery in Alzheimer's disease. Drug Discov Today Ther Strateg 10 (2), e85–e90.

Babiloni, C., Lizio, R., Del Percio, C., Marzano, N., Soricelli, A., Salvatore, E., Ferri, R., Cosentino, F.I.I., Tedeschi, G., Montella, P., Marino, S., De Salvo, S., Rodriguez, G., Nobili, F., Vernieri, F., Ursini, F., Mundi, C., Richardson, J.C., Frisoni, G.B., Rossini, P.M., 2013b. Cortical sources of resting state EEG rhythms are sensitive to the progression of early stage Alzheimer's disease. J Alzheimers Dis 34 (4), 1015–1035. https://doi.org/10.3233/JAD-121750

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

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

Berr, C., Balansard, B., Arnaud, J., Roussel, A.M., Alperovitch, A., 2000. Cognitive decline is associated with systemic oxidative stress: the EVA study. etude du vieillissement arteriel. J Am Geriatr Soc 48 (10), 1285–1291. https://doi.org/10.1111/j.1532-5415.2000.tb02603.x

Bonanni, L., Perfetti, B., Bifolchetti, S., Taylor, J.P., Franciotti, R., Parnetti, L., Thomas, A., Onofrj, M., 2015 Jan. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging 36 (1), 434–445. https://doi.org/10.1016/j.neurobiolaging.2014.07.009

Brown, L.M., Schinka, J.A., 2005. Development and initial validation of a 15-item informant version of the Geriatric Depression Scale. Int J Geriatr Psychiatry 20 (10), 911–918. https://doi.org/10.1002/gps.1375

Bugnicourt, J.-M., Godefroy, O., Chillon, J.-M., Choukroun, G., Massy, Z.A., 2013. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 24 (3), 353–363. https://doi.org/10.1681/asn.2012050536

Chao, C.T., Lai, H.J., Tsai, H.B., Yang, S.Y., Huang, J.W., COhort of GEriatric Nephrology in NTUH (COGENT) study group, 2017. Frail phenotype is associated with distinct quantitative electroencephalographic findings among end-stage renal disease patients: an observational study. BMC Geriatr 17 (1), 277. https://doi.org/10.1186/s12877-017-0673-3

Chen, T.K., Knicely, D.H., Grams, M.E., 2019. Chronic kidney disease diagnosis and management: a review. JAMA 322 (13), 1294–1304. https://doi.org/10.1001/jama.2019.14745

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

De Deyn, P.P., Vanholder, R., Eloot, S., Glorieux, G., 2009. Guanidino compounds as uremic (neuro)toxins. Semin Dial 22 (4), 340–345. https://doi.org/10.1111/j.1525-139X.2009.00577.x

Dossi, R.C., Nuñez, A., Steriade, M., 1992. Electrophysiology of a slow (0.5–4 Hz) intrinsic oscillation of cat thalamocortical neurones in vivo. J Physiol 447, 215–234. https://doi.org/10.1113/jphysiol.1992.sp018999

Fernandez, A., Arrazola, J., Maestu, F., Amo, C., Gil-Gregorio, P., Wienbruch, C., Ortiz, T., 2003. Correlations of hippocampal atrophy and focal low-frequency magnetic activity in Alzheimer disease: volumetric MR imaging magnetoencephalographic study. AJNR Am J Neuroradiol 24, 481–487.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Franko, E., Wehner, T., Joly, O., Lowe, J., Porter, M.C., Kenny, J., Thompson, A., Rudge, P., Collinge, J., Mead, S., 2016 Oct. Quantitative EEG parameters correlate with the progression of human prion diseases. J Neurol Neurosurg Psychiatry 87 (10), 1061–1067. https://doi.org/10.1136/jnnp-2016-313501

Gadewar, P., Acharya, S., Khairkar, P., Shukla, S., Mahajan, S.N., 2015. Dynamics of electroencephalogram (EEG) in different stages of chronic kidney disease. J Clin Diagn Res 9 (3). https://doi.org/10.7860/JCDR/2015/11257.5705

Go, A.S., Chertow, G.M., Fan, D., McCulloch, C.E., Hsu, C.Y., 2008. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13):1296-305. doi: 10.1056/NEJMoa041031. Erratum in: N Engl J Med 18 (4), 4.

Himmelfarb, J., 2009. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin Dial 22 (6), 636–643. https://doi.org/10.1111/j.1525-139X.2009.00659.x

Hughes, J.R., 1980. Correlations between EEG and chemical changes in uremia. Electroencephalogr Clin Neurophysiol 48 (5), 583–594. https://doi.org/10.1016/0013-4694(80)90293-x

Ikizler, T.A., Morrow, J.D., Roberts, L.J., et al., 2002. Plasma F2-isoprostane levels are elevated in chronic hemodialysis patients. Clin Nephrol 58 (3), 190–197. https://doi.org/10.5414/CNP58190

Jovicich, J., Babiloni, C., Ferrari, C., Marizzoni, M., Moretti, D.V., Del Percio, C., Lizio, R., Lopez, S., Galluzzi, S., Albani, D., Cavaliere, L., Minati, L., Didic, M., Fiedler, U., Forloni, G., Hensch, T., Molinuevo, J.L., Bartrés Faz, D., Nobili, F., Orlandi, D., Parnetti, L., Farotti, L., Costa, C., Payoux, P., Rossini, P.M., Marra, C., Schönknecht, P., Soricelli, A., Noce, G., Salvatore, M., Tsolaki, M., Visser, P.J., Richardson, J.C., Wiltfang, J., Bordet, R., Blin, O., Frisoniand, G.B., the PharmaCog Consortium, 2019. Two-year longitudinal monitoring of amnestic mild cognitive impairment patients with prodromal Alzheimer's disease using topographical biomarkers derived from functional magnetic resonance imaging and electroencephalographic activity. J Alzheimers Dis 69 (1), 15–35. https://doi.org/10.3233/JAD-180158

Kalimo, H., 2003. Does chronic brain edema explain the consequences of cerebral small-vessel disease? Stroke 34 (3), 806–812.

Killiany, R.J., Moss, M.B., Albert, M.S., Sandor, T., Tieman, J., Jolesz, F., 1993. Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease. Arch Neurol 50 (9), 949–954. https://doi.org/10.1001/archneur.1993.00540090052010

Kim, D.S., Kim, S.W., Gil, H.W., 2022. Emotional and cognitive changes in chronic kidney disease. Korean J Intern Med 37 (3), 489–501. https://doi.org/10.3904/kjim.2021.492. Epub 2022 Mar 8.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Rev 29, 169–195. https://doi.org/10.1016/s0165-0173(98)00056-3

Klimesch, W., 2012 Dec. α-Band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16 (12), 606–617. https://doi.org/10.1016/j.tics.2012.10.007. Epub 2012 Nov 7.

Lai, S., Mecarelli, O., Pulitano, P., Romanello, R., Davi, L., Zarabla, A., Mariotti, A., Carta, M., Tasso, G., Poli, L., Mitterhofer, A.P., Testorio, M., Frassetti, N., Aceto, P., Galani, A., Lai, C., 2016. Neurological, psychological, and cognitive disorders in patients with chronic kidney disease on conservative and replacement therapy. Medicine (Baltimore) 95 (48), e5191. https://doi.org/10.1097/MD.0000000000005191

Lai, S., Molfino, A., Mecarelli, O., Pulitano, P., Morabito, S., Pistolesi, V., Romanello, R., Zarabla, A., Galani, A., Frassetti, N., Aceto, P., Lai, C., 2018. Study Group on Geriatric Nephrology of the Italian Society of Nephrology. Neurological and Psychological Changes in Hemodialysis Patients Before and After the Treatment. Ther Apher Dial 22 (5), 530–538. https://doi.org/10.1111/1744-9987.12672

Latreille, V., Carrier, J., Gaudet-Fex, B., Rodrigues-Brazète, J., Panisset, M., Chouinard, S., Postuma, R.B., Gagnon, J.F., 2016. Electroencephalographic prodromal markers of dementia across conscious states in Parkinson's disease. Brain 139 (Pt 4), 1189–1199. https://doi.org/10.1093/brain/aww018

Levin, A., Stevens, P.E., 2011 28. Early detection of CKD: the benefits, limitations and effects on prognosis. Nat Rev Nephrol 7 (8), 446–457. https://doi.org/10.1038/nrneph.2011.86

Lim, Y.J., Sidor, N.A., Tonial, N.C., Che, A., Urquhart, B.L., 2021 13. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins (Basel) 13 (2), 142. https://doi.org/10.3390/toxins13020142

Lizio, R., Babiloni, C., Del Percio, C., Losurdo, A., Vernò, L., De Tommaso, M., Montemurno, A., Dalfino, G., Cirillo, P., Soricelli, A., Ferri, R., Noce, G., Pascarelli, M.T., Catania, V., Nobili, F., Famá, F., Orzi, F., Giubilei, F., Buttinelli, C., Triggiani, A.I., Frisoni, G.B., Scisci, A.M., Mastrofilippo, N., Procaccini, D.A., Gesualdo, L., 2018.

Different abnormalities of cortical neural synchronization mechanisms in patients with mild cognitive impairment due to Alzheimer's and chronic kidney diseases: an EEG study. J Alzheimers Dis 65 (3), 897–915. https://doi.org/10.3233/JAD-180245

Meyer, T.W., Hostetter, T.H., 2007. Uremia. N Engl J Med 357 (13), 1316–1325. https://doi.org/10.1056/NEJMra071313

Miglinas, M., Cesniene, U., Janusaite, M.M., 2020. Vinikovas A. Cerebrovascular disease and cognition in chronic kidney disease patients. Front Cardiovasc Med 7, 96. https://doi.org/10.3389/fcvm.2020.00096

Moretti, D.V., Miniussi, C., Frisoni, G., Zanetti, O., Binetti, G., Geroldi, C., Galluzzi, S., Rossini, P.M., 2007 Aug. Vascular damage and EEG markers in subjects with mild cognitive impairment. Clin Neurophysiol 118 (8), 1866–1876. https://doi.org/10.1016/j.clinph.2007.05.009

Natale, G., Calabrese, V., Marino, G., Campanelli, F., Urciuolo, F., de Iure, A., Ghiglieri, V., Calabresi, P., Bossola, M., Picconi, B., 2021. Effects of uremic toxins on hippocampal synaptic transmission: implication for neurodegeneration in chronic kidney disease. Cell Death Discov 7 (1), 295. https://doi.org/10.1038/s41420-021-00685-9

Novelli, G., Papagno, C., Capitani, E., Laiacona, M., Vallar, G., Cappa, S.F., 1986. Tre test clinici di ricerca e produzione lessicale. Taratura su sogetti normali. Arch Psicol Neurol Psichiatr 47, 477–506.

Osterrieth, P.A., 1944. Le test de copie d'une figure complexe. Arch Psychol 30, 206–356.

Pascual-Marqui, R.D., 2007. Discrete, 3D distributed, linear imaging methods of electric neuronal activity. Part 1: exact, zero error localization. Clin Neurophysiol 112, 845–852.

Peacock, M., 2021 Jan. Phosphate metabolism in health and disease. Calcif Tissue Int 108 (1), 3–15. https://doi.org/10.1007/s00223-020-00686-3

Peraza, L.R., Kaiser, M., Firbank, M., Graziadio, S., Bonanni, L., Onofrj, M., Colloby, S.J., Blamire, A., O'Brien, J., Taylor, J.P., 2014. fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. Neuroimage Clin 4, 558–565. https://doi.org/10.1016/j.nicl.2014.03.013

Peraza, L.R., Taylor, J.P., Kaiser, M., 2015. Divergent brain functional network alterations in dementia with Lewy bodies and Alzheimer's disease. Neurobiol Aging 36 (9), 2458–2467. https://doi.org/10.1016/j.neurobiolaging.2015.05.015

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

Reitan, R.M., 1958. Validity of the trail making test as an indicator or organic brain damage. Percept Mot Skills 8, 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Rodriguez, A.V., Funk, C.M., Vyazovskiy, V.V., Nir, Y., Tononi, G., Cirelli, C., 2016. Why does sleep slow-wave activity increase after extended wake? Assessing the effects of increased cortical firing during wake and sleep. J Neurosci 36 (49), 12436–12447. https://doi.org/10.1523/JNEUROSCI.1614-16.2016

Rosen, W.G., Terry, R.D., Fuld, P.A., Katzman, R., Peck, A., 1980. Pathological verification of ischemic score in differentiation of dementias. Ann. Neurol 7, 486–488. https://doi.org/10.1002/ana.410070516

Rroji, M., Figurek, A., Viggiano, D., Capasso, G., Spasovski, G., 2022. Phosphate in the context of cognitive impairment and other neurological disorders occurrence in chronic kidney disease. Int J Mol Sci 23 (13), 7362. https://doi.org/10.3390/ijms23137362

Sagales, T., Gimeno, V., Planella, M.J., Raguer, N., Bartolome, J., 1993. Effects of rHuEPO on Q-EEG and event-related potentials in chronic renal failure. Kidney Int 44, 1109–1115. https://doi.org/10.1038/ki.1993.356

Sarnak, M.J., Levey, A.S., Schoolwerth, A.C., Coresh, J., Culleton, B., Hamm, L.L., McCullough, P.A., Kasiske, B.L., Kelepouris, E., Klag, M.J., et al., 2003. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 108, 2154–2169.

Seliger, S.L., Longstreth Jr., W.T., 2008. Lessons about brain vascular disease from another pulsating organ, the kidney. Stroke 39 (1), 5–6. https://doi.org/10.1161/STROKEAHA.107.496000

Spence, J.D., Urquhart, B.L., 2022 Nov. Cerebrovascular disease, cardiovascular disease, and chronic kidney disease: interplays and influences. Curr Neurol Neurosci Rep 22 (11), 757–766. https://doi.org/10.1007/s11910-022-01230-6. Epub 2022 Oct 1.

Spinnler, H., Tognoni, G., 1987. Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 8, 1–120.

Stevens, P.E., Levin, A., 2013. Kidney disease: improving global outcomes chronic kidney disease guideline development work group members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 158 (11), 825–830. https://doi.org/10.7326/0003-4819-158-11-201306040-00007

Steriade, M., Llinás, R.R., 1988. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68, 649–742. https://doi.org/10.1152/physrev.1988.68.3.649

Wardlaw, J.M., Sandercock, P.A.G., Dennis, M.S., Starr, J., 2003. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke 34 (3), 806–811. https://doi.org/10.1161/01.STR.0000058480.77236.B3

Weiner, D.E., Bartolomei, K., Scott, T., Price, L.L., Griffith, J.L., Rosenberg, I., Levey, A.S., Folstein, M.F., Sarnak, M.J., 2009. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. Am J Kidney Dis 53 (3), 438–447. https://doi.org/10.1053/j.ajkd.2008.08.022