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Parietal resting-state EEG alpha source connectivity is associated with subcortical white matter lesions in HIV-positive people

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HIGHLIGHTS

- Parietal rsEEG alpha source connectivity is associated with subcortical white matter vascular lesions in HIV.
- This effect was also observed in HIV-positive persons with unimpaired cognition.
- MRI-rsEEG markers may be used to screen HIV-positive persons at risk of neurocognitive disorders.

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ABSTRACT

Objective: Parietal resting-state electroencephalographic (rsEEG) alpha (8–10 Hz) source connectivity is abnormal in HIV-positive persons. Here we tested whether this abnormality may be associated with subcortical white matter vascular lesions in the cerebral hemispheres.
Methods: Clinical, rsEEG, and magnetic resonance imaging (MRI) datasets in 38 HIV-positive persons and clinical and rsEEG datasets in 13 healthy controls were analyzed. Radiologists visually evaluated the subcortical white matter hyperintensities from T2-weighted FLAIR MRIs (i.e., Fazekas scale). In parallel, neurophysiologists estimated the eLORETA rsEEG source lagged linear connectivity from parietal cortical regions of interest.
Results: Compared to the HIV participants with no/negligible subcortical white matter hyperintensities, the HIV participants with mild/moderate subcortical white matter hyperintensities showed lower parietal interhemispheric rsEEG alpha lagged linear connectivity. This effect was also observed in HIV-positive persons with unimpaired cognition. This rsEEG marker allowed good discrimination (area under

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the receiver operating characteristic curve > 0.80) between the HIV-positive individuals with different amounts of subcortical white matter hyperintensities.
Conclusions: The parietal rsEEG alpha source connectivity is associated with subcortical white matter vascular lesions in HIV-positive persons, even without neurocognitive disorders.
Significance: Those MRI-rsEEG markers may be used to screen HIV-positive persons at risk of neurocognitive disorders.

1. Introduction

It is well known that human immunodeficiency virus (HIV) early invades the brain, probably by infected monocytes (Roberts et al., 2010; Williams et al., 2012), and causes neuropathological changes in 80–90% of the infected persons (Williams et al., 2012). Furthermore, 50–70% of HIV-positive (HIV) persons manifest neurologic and so-called HIV-associated neurocognitive disorders (HANDs), affecting episodic memory, attention, cognitive-motor, the speed of information processing, and frontal executive functions (Selnes, 2005).

Eyes-closed, resting-state electroencephalographic (rsEEG) rhythms reflect the neurophysiological regulation of vigilance, a fundamental brain function for supporting cognitive information processing (Babiloni et al., 2020). For this reason, these rsEEG rhythms were previously investigated in HIV over healthy participants; the spectral analysis of those rsEEG rhythms showed the following consistent abnormalities in the HIV groups: a widespread power density decrease at the alpha band (8–12 Hz; Gruzelier et al., 1996; Baldeweg and Gruzelier, 1997; Polich et al., 2000), often associated with a widespread power density increase at the delta (<4 Hz) and theta (4–7 Hz) bands (Itil et al., 1990). In contrast, the spectral coherence of rsEEG rhythms recorded at electrode pairs, as a rough model of functional cortical connectivity, gave inconsistent results: it showed increased (Newton et al., 1994) or decreased (Fletcher et al., 1997) alpha coherence in HIV persons with cognitive deficits when compared to controls.

A methodological limitation of the above rsEEG studies may be volume conduction effects spreading the cortical neural currents, which may cofound topographical and coherence analysis of rsEEG rhythms at scalp electrodes (Nuñez, 1995). To mitigate this limitation, we used the freeware called low-resolution brain electromagnetic tomography (LORETA; Pascual-Marqui et al., 1994) to estimate rsEEG cortical sources in HIV subjects. The main findings are summarized in the following. Treatment-Naïve HIV participants and those receiving a successful combined antiretroviral therapy (cART) were characterized by an abnormal increase and decrease in the rsEEG delta and alpha source activities, respectively, with maximum effects in the parietal regions (Babiloni et al., 2012, 2014, 2016a,b). The parietal intrahemispheric rsEEG alpha source connectivity was abnormal in the treatment-naïve HIV participants, mainly when cognitive deficits were observed (Babiloni et al., 2022). In interpreting those findings, we speculated that the abnormality of rsEEG alpha source connectivity might be due to subcortical white matter hyperintensities as an index of small vessel lesions in the cerebral hemispheres. These subcortical white matter hyperintensities were repeatably observed from T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRIs) recorded in HIV persons, especially when they had neurocognitive disorders, cerebrospinal fluid viral replication even with controlled plasma infection, and monocyte activation (Kuper et al., 2011; Peluso et al., 2012; Watson et al., 2017; Trentalange et al., 2020).

Here we used the general EEG methodology of the quoted study by Babiloni and colleagues (Babiloni et al., 2022) to test the exploratory hypothesis that the abnormalities of parietal rsEEG alpha source connectivity in HIV persons may be associated with substantial subcortical white matter hyperintensities in the supratentorial periventricular space and deeper regions of the cerebral hemispheres, these hyperintensities being supposed to probe a vascular lesion load (small vessel lesions mostly). To this aim, clinical, rsEEG, and MRI datasets from two Italian cohorts of HIV persons with different cognitive statuses were used. The subcortical white matter hyperintensities were evaluated through a visual analysis of T2-weighted FLAIR MRIs to stratify the HIV persons into one group with no or collectively negligible subcortical white matter vascular lesion load and another group with mild or moderate subcortical white matter vascular lesion load. The rsEEG source solutions were then contrasted between the HIV groups with different amounts of subcortical white matter vascular lesion load. Notably, standard visual scales to rate subcortical white matter vascular lesion load from MRIs were shown to produce consistent results in HIV persons (Robinson-Papp et al., 2018) and would be ideal for future routine clinical applications of rsEEG and MRI markers to prevent and early detect brain abnormalities in HIV persons at risk of cognitive decline.

2. Methods

2.1. Participants

The data analysis in the present retrospective study was based on clinical, neuropsychological, MRI, and rsEEG variables collected from 38 HIV participants recruited at the "Tor Vergata" University of Rome (N = 20; ROME clinical unit) and "Amedeo di Savoia" Hospital of Turin (N = 18; TURIN clinical unit). Furthermore, 13 control (Healthy) participants with intact cognition followed the clinical protocol used in the HIV participants except for the MRI recording. They were recruited at the ROME clinical unit. Concerning the enrolled HIV persons, the ROME cohort had a mean age of 41 years, a mini-mental state exam (MMSE) score of 29.4/30, and 265 of viral load (copies/ml), while the Turin cohort had a mean age of 53 years, a Mini-Addenbrooke's Cognitive Examination (MACE) score of 24.5/30, and 5.5 of viral load (copies/ml). See Supplementary materials, *Diagnostic criteria,* for a detailed description of the clinical diagnostic criteria, cognitive screening, and blood and urine sampling in line with the reference study by Babiloni and colleagues (Babiloni et al., 2022).

2.2. Magnetic resonance imaging (MRI) recordings and analysis

In the ROME clinical unit (University of Rome "Tor Vergata"), the MRIs were recorded in the HIV participants using a Philips Achieva 3T scanner. In comparison, they were recorded in the HIV participants using a Philips Ingenia 3T scanner in the TURIN clinical unit.

Three ROME clinical unit experts centrally analyzed the MRIs from the two clinical units as described in the following sections (Sapienza University of Rome; F.C., N.P., and C.P.). The 3D T1-weighted MRIs were visually inspected for artifacts and segmented into gray matter, white matter, and cerebrospinal fluid using the segmentation tool implemented in the Statistical Parametric Mapping 8 (SPM8; https://fil.ion.ucl.ac.uk/spm). For each HIV person, the intracranial volume was computed as the sum of gray matter, white matter, and cerebrospinal fluid volumes.

In the T2-weighted FLAIR MRIs, the segmentation of white matter hyperintensities, reflecting the (vascular) lesion load, was performed using the Lesion Segmentation Tool implemented in SPM8 (Schmidt et al., 2012). For each HIV person, the subcortical white matter (vascular) lesion load volume was extracted from their lesion load map and used in further analyses. The T2-weighted FLAIR MRIs were then registered to the standard-space MNI152 brain template (FSL; Jenkinson et al., 2002; Smith et al., 2004). The registration transforms were combined and applied to bring individual white matter lesion load maps into the MNI152 space.

The standard Fazekas scale (Fazekas et al., 1987) was used on the T2-weighted FLAIR MRIs to rate the subcortical white matter hyperintensities as an indicator of the vascular lesion load. This scale is based on the following scores: (i) for the periventricular white matter hyperintensities, 0 (no lesions), 1 (pencil-thin lining), 2 (smooth halo), and 3 (irregular with extension into deep white matter); (ii) for the deeper supratentorial white matter hyperintensities, 0 (no lesions), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent areas). The expert raters (N.P. and C.P.) assigned the Fazekas scale scores in blind on the demographic, clinical, and biomarker information on the HIV person examined and the clinical unit that collected the person's data.

To test the effect of the subcortical white matter (vascular) lesion load on the rsEEG source activations, the HIV participants were stratified into two groups. For each clinical unit (i.e., ROME and TURIN), one group was named "HIV group with a lower amount of white matter vascular lesion load in the cerebral hemispheres (HIV-LL-)." In comparison, the other was named "HIV group with a higher amount of white matter vascular lesion load in the cerebral hemispheres (HIV-LL+)." The assignment of the HIV persons to one of the above HIV-LL groups had to satisfy the following conditions: (i) the same number of HIV persons in the two groups; (ii) Fazekas-scale mean score significantly higher in the HIV-LL+ group than in the HIV-LL- group ($p < 0.05$, one tail); and (iii) matched age, sex, education, MMSE or MACE score, viral load, and CD4 count between the two HIV groups ($p > 0.05$ one tail). For more details, see Supplementary materials, Magnetic resonance imaging (MRI) recordings and analysis.

2.3. rsEEG recordings and preliminary data analysis

All participants (eyes-closed) rsEEG recordings lasted about 5 minutes (0.3–70 Hz bandpass, 256 Hz sampling frequency). The electrode montage included 19 scalp monopolar sensors placed following the 10–20 System. In parallel, horizontal and vertical electrooculograms (EOGs, 0.3–70 Hz bandpass, 256 Hz sampling frequency) were also collected.

The rsEEG data were off-line frequency-band passed at 0.1–45 Hz and divided into epochs of 2 seconds (i.e., 5 minutes = 150 epochs of 2 seconds). The rsEEG epochs contaminated by the muscular, ocular, head movements or non-physiological artifacts such as bad contact electrode-scalp were identified by an automated procedure (Moretti et al., 2003) and then unthinkingly checked and approved (or not) by two independent experimenters (G.N. and C.D.P).

Afterward, the artifact-free rsEEG epochs were used as an input to analyze the FFT-power spectrum with the Welch technique, Hanning windowing function, and no phase shift. The spectral power density from those data was performed with 0.5-Hz frequency resolution.

The following two frequency bands of interest were considered: delta and alpha. The ranges of those individual frequency bands were defined by the individual alpha frequency peak as follows: (i) delta band: individual alpha frequency minus 8 Hz – individual alpha frequency minus 6 Hz; (ii) alpha: individual alpha frequency minus 2 Hz – individual alpha frequency plus 2 Hz (for more details, see the reference study by Babiloni et al., 2022).

2.4. Estimation of rsEEG source activation and source connectivity

For the computation of the rsEEG source activation and source connectivity within the cortical compartment of a mathematical model of MRI-based head volume conductor (i.e., MNI-152), we used an improved version of LORETA freeware (Pascual-Marqui et al., 2002) called exact LORETA (eLORETA; Pascual-Marqui, 2007). Concerning the rsEEG source activations, for each participant and frequency band of interest (i.e., delta and alpha), the current density solutions were obtained at the frontal, central, parietal, occipital, and temporal macroregions of interest (ROIs) of the cortical source model. Concerning the rsEEG source connectivity, for each participant and individual frequency band of interest (i.e., delta and alpha), the lagged linear connectivity solutions were obtained for the following couples of sources: (i) parietal between the two hemispheres (interhemispheric), (ii) left parietal-frontal, parietal-central, parietal-occipital, and parietal-temporal, and (iii) right parietal-frontal, parietal-central, parietal-occipital, and parietal-temporal (see Supplementary Materials, *Estimation of rsEEG source activation and source connectivity* for more details).

2.5. Statistical analysis

Two main statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., https://www.statsoft.com). ANOVAs were computed using the eLORETA current density (rsEEG source activation) or lagged linear connectivity (rsEEG source connectivity) solutions as the dependent variables. Bonferroni test was used for post-hoc comparisons ($p < 0.05$, two-tailed). The results of the statistical analyses were controlled by the Grubbs test ($p < 0.01$) for the presence of outliers.

The first statistical session tested the control hypothesis that the rsEEG source activation at delta and alpha bands may differ between HIV-LL- and HIV-LL + groups. Two ANOVA (one for each clinical unit; ROME and TURIN) were computed using the eLORETA delta and alpha regional normalized source current density solutions as the dependent variable ($p < 0.01$). The ANOVAs used the following factors: Group (Healthy, HIV-LL-, and HIV-LL+), Band (delta and alpha), and ROI (frontal, central, parietal, occipital, and temporal).

The second statistical session tested the working hypothesis that the parietal rsEEG alpha source connectivity may differ between the HIV-LL- and HIV-LL+ groups. Four ANOVAs (two for each clinical unit; ROME and TURIN) were computed using the eLORETA lagged linear connectivity solutions as dependent variables ($p < 0.05$). Two ANOVAs assessed differences in the parietal interhemispheric lagged linear connectivity solutions between HIV-LL-and HIV-LL+ groups. The ANOVA for each clinical unit used the following factors: Group (Healthy, HIV-LL-, and HIV-LL+) and Band (delta and alpha). Two ANOVAs assessed differences in the

parietal intrahemispheric lagged linear connectivity solutions between HIV-LL-and HIV-LL+ groups. The ANOVA for each clinical unit used the following factors: Group (Healthy, HIV-LL-, and HIV-LL+), Hemisphere (right and left), Band (delta and alpha), and ROI-pair (parietal-frontal, parietal-central, parietal-occipital, and parietal-temporal).

3. Results

3.1. Demographic and clinical data

For each clinical unit (i.e., ROME and TURIN), Table 1 summarizes (i) the most relevant demographic characteristics (i.e., age, sex, and education attainment) and global cognitive status (i.e., MMSE or MACE score) observed in the Healthy, HIV-LL-, and HIV-LL+ groups; (ii) the HIV RNA viral load, CD4 lymphocyte count, subcortical white matter hyperintensity (lesion load) volume, and duration of cART therapy in the two HIV groups; (iii) the presence or absence of statistically significant differences ($p < 0.05$) between the three groups for the age, sex, educational attainment, and MMSE/MACE score; and (iv) the presence or absence of statistically significant differences ($p < 0.05$) between the HIV-LL- and HIV-LL+ groups for the HIV RNA viral load, CD4 lymphocyte count, and normalized subcortical white matter (vascular) lesion load. As expected and based on the stratification criterion, a statistically significant difference in the subcortical white matter (vascular) lesion load volume was found ($p < 0.001$). No other statistically significant differences were found ($p > 0.05$). Notably, all participants of the ROME clinical unit had a high mean MMSE score > 29, indicating a good global cognitive status. On the contrary, 8 HIV participants (i.e., 4 HIV-LL- and 4 HIV-LL +) of the TURIN clinical unit had a MACE score ≤ 25, indicating pathological global cognitive status. In the Supplementary materials, *Neuropsychological data,* we reported the detailed results of the neuropsychological tests).

3.2. MRI data

Table 2 reports the Fazekas scale score for each HIV participant. For the ROME clinical unit, the HIV-LL- group (N = 10) was characterized by a Fazekas-scale mean score of 0 (±0 SD). In contrast, the HIV-LL + group (N = 10) showed a Fazekas-scale mean score of 1.1 (±0.3 SD), which reflected mild (vascular) lesion load in all HIV persons of the group. For the TURIN clinical unit, the HIV-LL- group (N = 8) was characterized by a Fazekas-scale mean score of 0.8 (±0.4 SD), which reflected no or mild (vascular) lesion load in the HIV persons of the group. The HIV-LL + group (N = 8) showed a Fazekas-scale mean score of 1.6 (±0.7 SD), which reflected white matter mild or moderate (vascular) lesion load in the HIV persons of the group. For the sake of communication simplicity, we referred to the HIV-LL- groups as collectively characterized by "negligible" subcortical white matter (vascular) lesion load and to the HIV-LL + groups as collectively characterized by "mild" subcortical white matter (vascular) lesion load.

We tested a control hypothesis of statistical differences in the normalized white matter, gray matter, and cerebrospinal fluid volumes between the HIV-LL- and HIV-LL + groups for each clinical unit ($p < 0.05$ uncorrected). Those MRI markers were square root transformed to make them Gaussian. T-tests were computed. No statistically significant differences were found ($p > 0.05$; Table S2).

A control analysis tested that the Mann-Whitney U test for each clinical unit (i.e., ROME and TURIN) evaluated the presence or absence of statistically significant differences between the HIV-LL- and HIV-LL + groups for the Fazekas scores. As expected, a statistically significant difference (HIV-LL- < HIV-LL +) was found for both clinical units (ROME: $p < 0.001$; TURIN: $p < 0.05$). Other control analyses showed that the subcortical white matter (vascular) lesion load statistical maps showed greater hyperintensity in the perivascular regions in the HIV-LL + than and HIV-LL- groups ($p < 0.05$ uncorrected; Fig. S1). Furthermore, the total gray matter,

Table 1
Mean values (±standard error mean, SE) of the following variables of interest for each clinical unit (i.e., ROME and TURIN): (i) the demographic characteristics and global cognitive status (MMSE/MACE score) and results of their statistical comparisons ($p < 0.05$) in the demographic-matched groups of cognitively normal (Healthy), human immunodeficiency virus-positive (HIV) with a lower amount of subcortical white matter (vascular) lesion load (HIV-LL-), and HIV-positive with a higher amount of subcortical (vascular) white matter lesion load (HIV-LL +) persons; (ii) the clinical features (i.e., HIV RNA viral load and CD4 lymphocyte count), and results of their statistical comparisons ($p < 0.05$) in the HIV-LL- and HIV-LL + groups; and (iii) the subcortical white matter (vascular) lesion load volume and results of their statistical comparisons ($p < 0.05$) in the HIV-LL- and HIV-LL + groups. The subcortical white matter (vascular) lesion load volume was estimated from the hyperintensities of the T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRIs). It was normalized with respect to the total intracranial volume. Legend: MMSE, Mini-Mental State Evaluation; MACE, Mini-Addenbrooke's Cognitive Examination; M/F, males/females; and n.s., not statistically significant ($p > 0.05$). For the sake of communication simplicity, we referred to the HIV-LL- groups as collectively characterized by "negligible" subcortical white matter (vascular) lesion load and to the HIV-LL + groups as collectively characterized by "mild" subcortical white matter (vascular) lesion load.

DEMOGRAPHIC CHARACTERISTICS AND CLINICAL DATA				
ROME CLINICAL UNIT				
	Healthy	HIV-LL-	HIV-LL+	Statistical analysis
N	13	10	10	-
Age (years)	42.6 (±3.6 SE)	40.2 (±2.8 SE)	42.0 (±3.7 SE)	ANOVA: n.s.
Sex (F/M)	1/12	2/8	3/7	Freeman Halton test: n.s.
Education (years)	12.4 (±1.0 SE)	13.9 (±1.0 SE)	13.2 (±1.2 SE)	ANOVA: n.s.
MMSE	29.7 (±0.2 SE)	29.4 (±0.3 SE)	29.4 (±0.4 SE)	Kruskal Wallis ANOVA test: n.s.
Viral load (copies/ml)	-	211 (±140 SE)	308 (±239 SE)	T-test: n.s.
CD4 (cells/μl)	-	433 (±325 SE)	499 (±113 SE)	T-test: n.s.
Lesion load volume (cm^3)	-	0.00015 (±0001 SE)	0.0016 (±0005 SE)	T-test: $p < 0.001$
TURIN CLINICAL UNIT				
	HIV-LL-	HIV-LL+		Statistical analysis
N	9	9		
Age (years)	52.7 (±1.8 SE)	53.9 (±2.7 SE)		T-test: n.s.
Sex (F/M)	3/6	2/7		Fisher test: n.s.
Education (years)	10.6 (±1.1 SE)	9.5 (±2.1 SE)		T-test: n.s.
MACE	25.0 (±1.7 SE)	23.6 (±1.8 SE)		Mann-Whitney U test: n.s.
Viral load(copies/ml)	4 (±4 SE)	7 (±4 SE)		T-test: n.s.
CD4 (cells/μl)	876 (±235SE)	660 (±60 SE)		T-test: n.s.
Lesion load volume (cm^3)	0.0005 (±0001 SE)	0.0033 (±0008 SE)		T-test: $p < 0.001$

Table 2
Fazekas scale score for each HIV participant of the two clinical units (i.e., ROME and TURIN). Legend: HIV, human immunodeficiency virus; HIV-LL-, HIV-positive with a lower amount of subcortical white matter (vascular) lesion load; HIV-LL+, HIV-positive with a higher amount of subcortical white matter (vascular) lesion load.

MRI DATA	
ROME CLINICAL UNIT Subjects	Fazekas score
HIV-LL- #01	0
HIV-LL- #02	0
HIV-LL- #03	0
HIV-LL- #04	0
HIV-LL- #05	0
HIV-LL- #06	0
HIV-LL- #07	0
HIV-LL- #08	0
HIV-LL- #09	0
HIV-LL- #10	0
HIV-LL+ #01	1
HIV-LL+ #02	2
HIV-LL+ #03	1
HIV-LL+ #04	1
HIV-LL+ #05	1
HIV-LL+ #06	1
HIV-LL+ #07	1
HIV-LL+ #08	1
HIV-LL+ #09	1
HIV-LL+ #10	1
TURIN CLINICAL UNIT Subjects	Fazekas score
HIV-LL- #01	1
HIV-LL- #02	0
HIV-LL- #03	1
HIV-LL- #04	0
HIV-LL- #05	1
HIV-LL- #06	1
HIV-LL- #07	1
HIV-LL- #08	1
HIV-LL- #09	1
HIV-LL+ #01	1
HIV-LL+ #02	2
HIV-LL+ #03	2
HIV-LL+ #04	1
HIV-LL+ #05	1
HIV-LL+ #06	1
HIV-LL+ #07	2
HIV-LL+ #08	1
HIV-LL+ #09	3

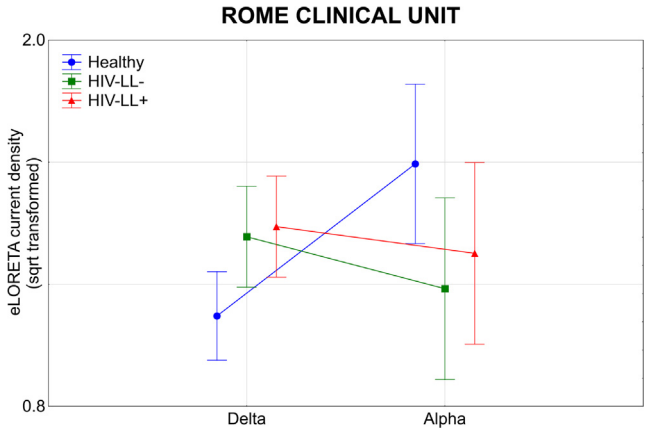

Fig. 1. Mean values (±SE) of the exact low-resolution brain electromagnetic tomography (eLORETA) regional normalized current density solutions (square root transformed) from resting-state electroencephalographic (rsEEG) rhythms relative to a statistically significant ANOVA interaction effect ($F = 8.5$; $p < 0.001$) between the factors Group (Healthy, HIV-LL-, and HIV-LL +) and Band (delta and alpha) for the ROME clinical unit. Legend: Healthy, HIV-negative and cognitively unimpaired; HIV-LL-, HIV-positive with a lower amount of subcortical white matter (vascular) lesion load; HIV-LL+, HIV-positive with a higher amount of subcortical white matter (vascular) lesion load. The subcortical white matter (vascular) lesion load was estimated from the hyperintensities of the T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRIs). For the sake of communication simplicity, we referred to the HIV-LL- groups as collectively characterized by "negligible" subcortical white matter (vascular) lesion load and to the HIV-LL + groups as collectively characterized by "mild" subcortical white matter (vascular) lesion load.

the total white matter, and the total cerebrospinal matter volumes did not differ between the HIV-LL + and HIV-LL- groups ($p > 0.05$ uncorrected; Table S2). We reported more details on these results in the Supplementary materials, Magnetic resonance imaging (MRI) recordings and analysis.

3.3. eLORETA regional normalized source current density solutions

For the ROME clinical unit, the ANOVA evaluating the differences in the eLORETA regional normalized source current density solutions (square root transformed) from rsEEG rhythms among the Healthy, HIV-LL-, and HIV-LL + groups showed a statistically significant interaction effect ($F = 8.5$; $p < 0.001$; Fig. 1) between the factors Group (Healthy, HIV-LL-, and HIV-LL +) and Band (delta and alpha). Bonferroni post-hoc testing ($p < 0.05$) did not show the eLORETA discriminant regional normalized source current density pattern HIV-LL- ≠ HIV-LL+ ($p > 0.05$). Furthermore, Bonferroni post-hoc testing ($p < 0.05$) unveiled *the* discriminant normalized source current density pattern Healthy ≠ HIV-LL- and HIV-LL + at the alpha band (Healthy > HIV-LL $p = 0.04$; Healthy < HIV-LL+: $p = 0.03$).

For the TURIN clinical unit, the ANOVA evaluating the differences in the eLORETA regional normalized source current density solutions (square root transformed) from rsEEG rhythms among the HIV-LL- and HIV-LL + groups did not show statistically significant results ($p > 0.05$).

These findings were not due to outliers from the eLORETA regional normalized source current density solutions (square root transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

The results showed that the rsEEG delta and alpha source activation did not differ as a function of the white matter lesion load in the HIV participants.

3.4. eLORETA interhemispheric and intrahemispheric lagged linear connectivity solutions

For the ROME clinical unit, the ANOVA evaluating the differences in the eLORETA parietal interhemispheric lagged linear connectivity solutions (square root transformed) from the rsEEG rhythms among the Healthy, HIV-LL-, and HIV-LL + groups showed a significant interaction effect ($F = 5.2$; $p < 0.01$; Fig. 2 top) for the factors Group (Healthy, HIV-LL-, and HIV-LL +) and Band (delta and alpha). Bonferroni post-hoc testing ($p < 0.05$) revealed the eLORETA discriminant interhemispheric lagged linear connectivity pattern HIV-LL- ≠ HIV-LL+ (HIV-LL- > HIV-LL +) at the alpha frequencies ($p = 0.04$). Furthermore, Bonferroni post-hoc testing ($p < 0.05$) unveiled the eLORETA discriminant interhemispheric lagged linear connectivity pattern Healthy ≠ HIV-LL+ (Healthy > HIV-LL +) at the alpha frequencies ($p = 0.000001$).

The ANOVA evaluating the differences in the eLORETA parietal intrahemispheric lagged linear connectivity solutions (square root transformed) from rsEEG rhythms among the Healthy, HIV-LL-, and HIV-LL + groups showed a significant interaction effect ($F = 3.4$; $p < 0.05$; Fig. 2 bottom) for the factors Group and Band. Bonferroni post-hoc testing ($p < 0.05$) unveiled the eLORETA discriminant

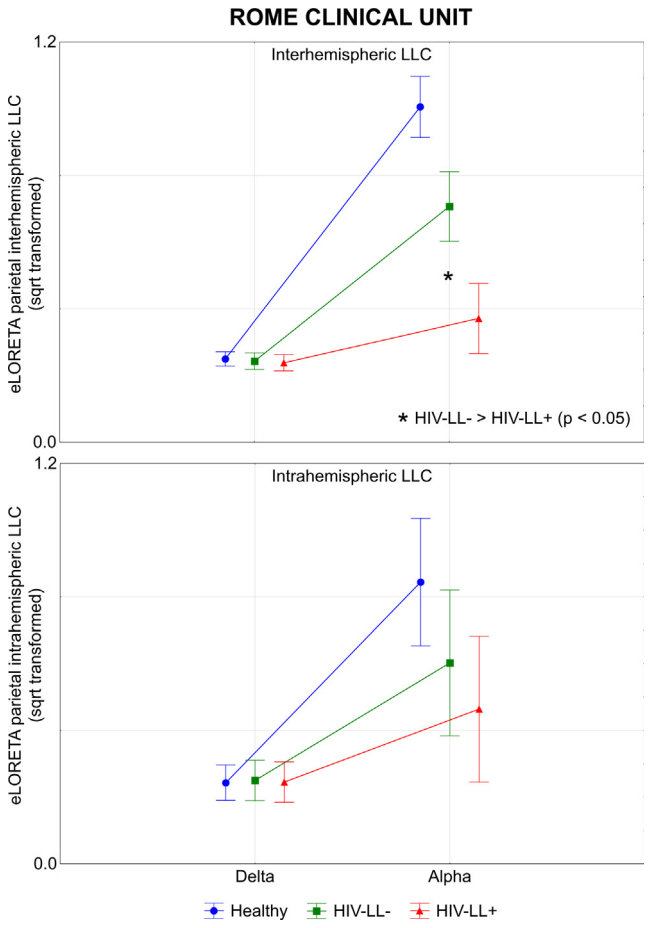

Fig. 2. (Top): Mean values (±SE) of the eLORETA parietal interhemispheric lagged linear connectivity solutions from rsEEG rhythms relative to a statistically significant ANOVA interaction effect ($F = 5.2$; $p < 0.01$) between the factors Group (Healthy, HIV-LL-, and HIV-LL +) and Band (delta and alpha) for the ROME clinical unit. (Bottom): Mean values (±SE) of the eLORETA parietal intrahemispheric lagged linear connectivity solutions from rsEEG rhythms relative to a statistically significant ANOVA interaction effect ($F = 3.4$; $p < 0.05$) between the factors Group (Healthy, HIV-LL-, and HIV-LL +) and Band (delta and alpha) for the ROME clinical unit. The asterisk indicates the rsEEG frequency bands in which the rsEEG lagged linear connectivity solutions presented the statistically significant pattern: HIV-LL- ≠ HIV-LL+ ($p < 0.05$, Bonferroni post-hoc). Legend: eLORETA, exact low-resolution brain electromagnetic tomography; LLC, lagged linear connectivity; Healthy, cognitively normal; HIV-LL-, HIV-positive with a lower amount of subcortical white matter lesion load; and HIV-LL+, HIV-positive with a higher amount of subcortical white matter (vascular) lesion load.

intrahemispheric lagged linear connectivity pattern Healthy ≠ HIV-LL- and HIV-LL+ (Healthy > HIV-LL- >: $p = 0.002$; Healthy > HIV-LL+: $p = 0.0006$). Furthermore, post-hoc testing showed a trend for an eLORETA discriminant intrahemispheric lagged linear connectivity pattern HIV-LL- > HIV-LL+ ($p > 0.05$ corrected).

For the TURIN clinical unit, the ANOVA evaluating the differences in the eLORETA parietal interhemispheric lagged linear connectivity solutions (square root transformed) from the rsEEG rhythms between the HIV-LL- and HIV-LL + groups showed a significant interaction effect ($F = 6.4$; $p < 0.05$; Fig. 3) for the factors Group (HIV-LL- and HIV-LL +) and Band (delta and alpha). Bonferroni post-hoc testing ($p < 0.05$) revealed the eLORETA discriminant interhemispheric lagged linear connectivity pattern HIV-LL- ≠ HIV-LL+ (HIV-LL- > HIV-LL +) at the alpha frequencies ($p = 0.04$).

The ANOVA evaluating the differences in the eLORETA parietal intrahemispheric lagged linear connectivity solutions (square root transformed) from rsEEG rhythms between the HIV-LL- and HIV-LL + groups did not show statistically significant results ($p > 0.05$).

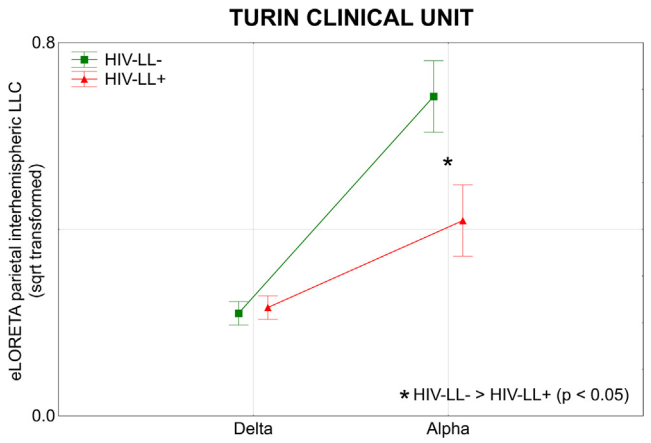

Fig. 3. Mean values (±SE) of the eLORETA parietal interhemispheric lagged linear connectivity solutions from rsEEG rhythms relative to a statistically significant ANOVA interaction effect ($F = 6.4$; $p < 0.05$) between the factors Group (HIV-LL- and HIV-LL +) and Band (delta and alpha) for the TURIN clinical unit. The asterisk indicates the rsEEG frequency bands in which the rsEEG lagged linear connectivity solutions presented the statistically significant pattern: HIV-LL- ≠ HIV-LL+ ($p < 0.05$, Bonferroni post-hoc). Legend: eLORETA, exact low-resolution brain electromagnetic tomography; HIV, human immunodeficiency virus; rsEEG, resting-state electroencephalographic; LLC, lagged linear connectivity; HIV-LL-, HIV-positive with a lower amount of subcortical white matter lesion load; and HIV-LL +, HIV-positive with a higher amount of subcortical white matter (vascular) lesion load.

These findings were not due to outliers from the parietal rsEEG lagged linear connectivity solutions (square root transformed), as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$.

The present results unveiled that the parietal interhemispheric rsEEG alpha (but not delta) source connectivity differed as a function of the white matter lesion load in the HIV participants.

3.5. Control analyses

We performed additional control analyses to understand the core results better. These control analyses showed that: (i) the eLORETA parietal interhemispheric rsEEG alpha lagged linear connectivity differences between the HIV-LL- and HIV-LL + groups were also observed considering together the HIV participants of the ROME and TURIN clinical units ($p < 0.0001$; Fig. S2); (ii) the eLORETA parietal interhemispheric rsEEG alpha lagged linear connectivity solutions allowed a good classification accuracy between HIV-LL- and HIV-LL + individuals for each clinical unit (area under the receiver operating characteristic curve > 0.80; Fig. S3); and (iii) the eLORETA parietal interhemispheric rsEEG alpha lagged linear connectivity (square root transformed) unveiled a statistically significant negative correlation with the subcortical white matter (vascular) lesion load volume in the HIV individuals for each clinical unit (Spearman test; ROME clinical unit: $R = -0.47$, $p < 0.05$; TURIN clinical unit: -0.55, $p < 0.01$; Fig. 4). The higher the eLORETA parietal interhemispheric lagged linear connectivity, the lower the white matter lesion load volume. We reported more details on these results in the Supplementary Materials, *Control analyses on the parietal interhemispheric rsEEG alpha source connectivity.*

4. Discussion

This retrospective and exploratory study investigated whether parietal rsEEG alpha source connectivity abnormalities may be associated with supratentorial subcortical white matter vascular lesions in HIV subjects.

The present findings showed that the parietal interhemispheric rsEEG alpha source connectivity was more abnormal in the HIV

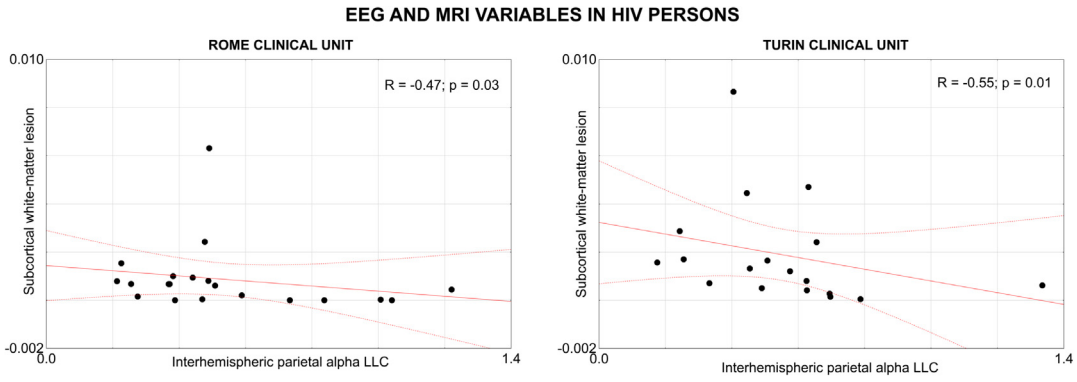

Fig. 4. Scatterplot showing the correlation between the eLORETA parietal interhemispheric lagged linear connectivity (square root transformed) from the rsEEG rhythms and the subcortical white matter (vascular) lesion load volumes in the HIV-positive participants for each clinical unit (i.e., ROME and TURIN). The Spearman test evaluated the hypothesis of a correlation between the above two variables ($p < 0.05$). Legend: eLORETA, exact low-resolution brain electromagnetic tomography; rsEEG, resting-state electroencephalographic; HIV, human immunodeficiency virus; LLC, lagged linear connectivity.

group with mild (over negligible) subcortical white matter vascular lesions in the cerebral hemispheres as revealed by the visual analysis of the T2-weighted FLAIR MRIs using the Fazekas scale. Furthermore, the parietal interhemispheric rsEEG alpha source connectivity allowed a good discrimination accuracy in detecting HIV participants with substantial subcortical white matter vascular lesions (>80%). Interestingly, the above results were also observed considering only the HIV participants with normal global cognitive status.

The present results complement previous evidence showing abnormal subcortical white matter hyperintensities from T2-weighted FLAIR MRIs in HIV persons, especially when they were characterized by neurocognitive disorders, cerebrospinal fluid viral replication even with controlled plasma infection, and monocyte activation (Kuper et al., 2011; Peluso et al., 2012; Watson et al., 2017; Trentalange et al., 2020). Furthermore, present results illuminate previous evidence suggesting the possible neurophysiological consequence of the abnormal subcortical white matter hyperintensities possibly reflecting small vessel lesions in the cerebral hemispheres. Those vascular lesions might induce poor parietal interhemispheric rsEEG alpha source connectivity in HIV persons, possibly impacting the neurophysiological regulation of vigilance and cognitive processes. Along this speculative line, previous rsEEG studies in old persons with (non-HIV) dementia may provide a useful conceptual frame.

Those studies compared the mathematical inter-relatedness of the rsEEG rhythms between electrode pairs in patients with (non-HIV) dementia due to Alzheimer's and cerebrovascular diseases as rough measures of the brain functional connectivity underpinning the regulation of the quiet vigilance and cognition (Leuchter et al., 1992, 1994a,b). The results of these studies showed that (non-HIV) patients with dementia due to subcortical vascular lesions in the periventricular white matter manifested poor rsEEG spectral coherence at centroparietal electrode pairs (overlying those lesions) for several frequency bands, including alpha, with relatively spared spectral coherence at distant frontal-parietooccipital electrode pairs. In contrast, patients with Alzheimer's disease dementia, typically due to cortical gray-matter neurodegeneration, exhibited poor rsEEG spectral coherence at remote frontal-parietooccipital electrode pairs (Leuchter et al., 1992, 1994a,b). Along the same line, patients with dementia due to cerebrovascular disease showed fewer abnormalities in the rsEEG synchronization likelihood (i.e., a measure sensitive to both linear and nonlinear interrelatedness of rsEEG activity) computed at distant frontal-parietal electrode pairs for several frequencies, including alpha (Babiloni et al., 2004). Furthermore, Alzheimer's disease patients with mild cognitive impairment and significant subcortical white matter vascular lesions were characterized by minor abnormalities in the directed transfer function (i.e., a multivariate measure derived from Granger causality sensitive to linear directional interrelatedness of rsEEG activity) computed from parietal to frontal electrodes (Babiloni et al., 2008a, 2008b).

Overall, the previous and present findings suggest that even before objective cognitive deficits, HIV patients with controlled viremia and acceptable immunoreactivity may have specific subcortical white matter vascular lesions that affect relatively local parietal interhemispheric functional connectivity during quiet wakefulness. At very early stages of this functional dysconnectivity in the parietal cortex, standard "paper and pencil" neuropsychological and clinical tests may not be sensitive enough to detect a subtle "parietal" syndrome slightly affecting mood, spatial awareness (orientation), visual attention (neglect), and other cognitive-motor (apraxia) functions. Therefore, developing and validating computerized procedures to test parietal functions in HIV persons are recommended. In this direction, a recent review reported that eight digital tools implemented on smartphones, tablets, or computers (e.g., Cogstate, Neuroscreen, California Computerized Assessment Package, etc.) showed substantial validity in the neuropsychological and affective assessment of HIV persons in < 30 minutes, using the standard "paper and pencil" neuropsychological and clinical tests as the gold standard (Wilson et al., 2023). These tools are a good basis to address the unmet need to validate them to detect subtle cognitive and affective deficits unrevealed by standard "paper and pencil" neuropsychological and clinical tests. Indeed, a recent extensive literature review reported a mean prevalence of 23.5% asymptomatic neurocognitive impairment (i.e., cognitive deficits with unimpaired autonomy in the activities of daily living), 13.3% mild neurocognitive disorder, and 5.0% HIV-associated dementia according to the Frascati criteria (Wang et al., 2020). These data suggest that most cognitive burdens may be in the gray zone between mild and mild cognitive impairment. For this purpose, the present MRI-EEG biomarkers of the present study may be the gold standard for validating the mentioned new generation of digital tools for assessing the preclinical parietal syndrome in HIV persons with normal cognitive status based on traditional neuropsychological and clinical tests.

4.1. Methodological remarks

The following methodological limitations should be considered in evaluating the present results. First, we enrolled a relatively small number of HIV participants (N = 38). Second, intrinsic limita-

tions of the reference database made possible just a cross-modal design focused on a single recording session. Third, we used an electrode montage with only 19 scalp electrodes (e.g., 10–20 montage system) for the EEG recordings, which is a clinical suboptimal spatial sampling of the EEG activity for source estimation (Liu et al., 2002; Hassan et al., 2014; Sohrabpour et al., 2015; Marino et al., 2016). Fourth, the subcortical white matter hyperintensities from T2-weighted FLAIR MRIs are clinically relevant in HIV-positive persons. However, they are nonspecific for HIV, depending on age, blood hypertension, components of the social environment (i.e., widowed, living alone), prediabetes and hepatic function, etc. (Grosu et al., 2021). Furthermore, we did not consider the white matter lesion load in the cerebral cortex and brainstem despite its relevance in HIV based on previous studies using the voxel-based morphometry analysis of MRIs (Kuper et al., 2011; Joy et al., 2023). The main focus of the present study was the use of MRI procedures currently used in routine clinical practice for potential future large-scale applications of the MRI-EEG markers tested here.

5. Conclusions

In the present exploratory study, we tested the hypothesis that parietal rsEEG alpha source connectivity abnormalities may be associated with subcortical white matter vascular lesions rated from T2-weighted FLAIR MRIs in HIV persons.

Compared to the HIV group with negligible subcortical white matter hyperintensities reflecting those lesions, the HIV group with mild subcortical white matter hyperintensities showed lower parietal interhemispheric rsEEG alpha lagged linear connectivity. This effect was also observed in HIV persons with unimpaired cognition. Those rsEEG markers allowed good discrimination (area under the receiver operating characteristic curves > 0.80) between the HIV-positive individuals of the two groups.

These results show that parietal interhemispheric rsEEG alpha source connectivity is associated with subcortical white matter vascular lesions in HIV-positive persons, even without neurocognitive disorders.

Future longitudinal and prospective studies using larger sample sizes should test if the combination of the present MRI and rsEEG biomarkers could detect HIV persons with very early subtle cognitive and affective disorders potentially unrecognized by standard neuropsychological and clinical tests.

Conflict of Interest Statement

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

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The hypothesis and results of the present paper are original and unpublished, as it is the first time we tested the relationship between resting-state EEG rhythms and MRIs probing subcortical white-matter (vascular) lesion load in HIV-positive persons. To make comparable the current results with those of a previous EEG study of our group carried out in HIV-positive persons (Babiloni et al., Brain Res Bull. 2022;181: 129-143), we used the same methodologies for the collection and analysis of clinical and EEG data of that study. To emphasize the use of the same methodology, some paragraphs of the "Methods" in the present paper report the identical wording used in the previous study. Notably, no HIV dataset from that previous study was employed in the present investigation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2023.09.006.

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