



Article scientifique

Article

2024

Published version

Open Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Alterations in gamma frequency oscillations correlate with cortical tau deposition in Alzheimer's disease

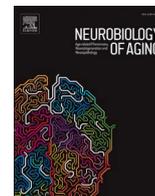
Nencha, Umberto; Rigoni, Isotta; Ribaldi, Federica; Altomare, Daniele; Seeck, Margitta; Garibotto, Valentina; Vulliemoz, Serge; Frisoni, Giovanni

How to cite

NENCHA, Umberto et al. Alterations in gamma frequency oscillations correlate with cortical tau deposition in Alzheimer's disease. In: Neurobiology of aging, 2024, vol. 139, p. 1–4. doi: 10.1016/j.neurobiolaging.2024.03.008

This publication URL: <https://archive-ouverte.unige.ch/unige:177370>

Publication DOI: [10.1016/j.neurobiolaging.2024.03.008](https://doi.org/10.1016/j.neurobiolaging.2024.03.008)



Brief Communication

Alterations in gamma frequency oscillations correlate with cortical tau deposition in Alzheimer's disease

Umberto Nench^{a,c,*}, Isotta Rigoni^{b,1}, Federica Ribaldi^{a,c}, Daniele Altomare^{a,c,d,e}, Margitta Seeck^b, Valentina Garibotto^{f,g,h}, Serge Vulliémoz^b, Giovanni B. Frisoni^{a,c}

^a Geneva Memory Center, Division of Geriatrics, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland

^b EEG and Epilepsy Unit, Division of Neurology, Department of Clinical Neurosciences, University Hospitals and Faculty of Medicine of University of Geneva, Geneva, Switzerland

^c Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland

^d Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

^e Neurology Unit, ASST Spedali Civili, Brescia, Italy

^f Division of Nuclear Medicine and Molecular Imaging, Department of Diagnostics, Geneva University Hospitals, Geneva, Switzerland

^g NIMTLab, Faculty of Medicine, University of Geneva, Geneva, Switzerland, Geneva, Switzerland

^h Center for Biomedical Imaging (CIBM), Geneva, Switzerland



ARTICLE INFO

Keywords:

Alzheimer's disease
Tau
PET
Gamma oscillations
EEG

ABSTRACT

We assessed the relationship of gamma oscillations with tau deposition in Alzheimer's disease (AD) and other cognitive diseases, as both are altered during the disease course and relate to neurodegeneration. We retrospectively analyzed data from 7 AD, tau positive patients and 9 tau negative patients, who underwent cerebral amyloid PET and tau PET, and EEG within 12 months. Relative gamma power was higher in tau positive (AD) patients than in tau negative patients ($p < .05$). In tau positive AD patients, tau burden was associated with a linear increase in gamma power ($p < .05$), while no association was present in the tau negative group nor with amyloid- β burden in either group. Thus, increase in the gamma power might represent a novel biomarker for tau driven neurodegeneration.

1. Introduction

Alzheimer's Disease (AD) is the most prevalent cause of dementia worldwide (Anon, 2021) and its prevalence is expected to increase during the next years. The hallmarks of AD are progressive amyloid- β (A β) plaques and neurofibrillary tangles (tau) deposition, and the latter correlates with clinical symptoms, disease severity and speed of progression (Digma et al., 2019; Pontecorvo et al., 2017). Currently, the only way to assess in-vivo tau deposition is through either lumbar puncture or cerebral tau PET. In AD, gamma oscillations (> 30 Hz) show early alterations in the disease course (Verret et al., 2012; Wang et al., 2017). Here, we explored the alterations in the gamma band as proxies of cortical tau deposition in a memory clinic population.

2. Methods

2.1. Patients

We analyzed data of 7 AD patients with significant amyloid and tau deposition and 9 patients with either a subjective cognitive decline or objective cognitive deficits without tau deposition from the Geneva Memory Center. We included patients who underwent cerebral tau PET and a low-density resting-state EEG within 12 months. This study was approved by the local ethics committee and has been conducted in accordance with the principles of the Declaration of Helsinki (PB_2016-01382 (15-206)).

Abbreviations: AD, Alzheimer's disease; PET, positron emission tomography; SUVr, standard uptake value ratio; EEG, electroencephalography; A β 42, amyloid-beta 42.

* Correspondence to: Centre de la Mémoire, Service de Gériatrie, Département de Gériatrie et Réadaptation, Hôpitaux Universitaires de Genève, rue Gabrielle Perret-Gentil 6, Genève 1205, Switzerland.

E-mail address: umne@hcuge.ch (U. Nench).

¹ U. Nench and I. Rigoni share equal contributions.

<https://doi.org/10.1016/j.neurobiolaging.2024.03.008>

Received 17 July 2023; Received in revised form 27 March 2024; Accepted 27 March 2024

Available online 30 March 2024

0197-4580/© 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

2.2. EEG acquisition and analysis

We selected 5 min of the clinical low-density resting state EEG (eyes-opened and closed, 25-channel, sampling rate = 256 Hz). The signal was band-pass filtered ([1–100 Hz]) and notch-filtered at 50 and 100 Hz. Sensors with poor signal-to-noise ratio were removed and interpolated. Independent component analysis and further visual inspection was performed to remove eye blinks and muscle artifacts, after which data were re-referenced to the average. The remaining signal was cropped into epochs of 1 s without overlap (Table 1). The power spectral density was calculated using a single Hanning taper and, for each EEG channel, the relative power in gamma band was defined as the percentage of the power between 30 and 98 Hz with respect to the total power. For statistical analyses, we used both the relative gamma power calculated for each channel and also averaged over the 25 sensors. EEG analyses were carried out in Matlab.

2.3. PET images acquisition and analysis

PET images were realized using a Siemens Biograph mCT or Vision PET scanner. Cerebral tau-PET images were acquired using ¹⁸F-Flortaucipir and amyloid-PET images were acquired using ¹⁸F-Flutemetamol (N = 14) or ¹⁸F-Florbetapir (N = 2). Global tau-PET SUVR was computed as previously described (Mishra et al., 2017), while tau and amyloid status (positive or negative) were assessed visually by an expert nuclear medicine physician (GV) following validated recommendations (Fleisher et al., 2020). Subjects were classified as positive when they showed a significant uptake of the tracer (a confluent area higher than 65% of the average uptake measured in the cerebellum) in the posterolateral temporal, occipital or parietal/precuneus region in either hemisphere.

2.4. Statistical analyses

Differences in demographical and clinical data across tau-positive (tau-P) and tau-negative (tau-N) patients were assessed using Mann-Whitney U and Chi-squared test for continuous and categorical variables, respectively. The relative gamma power (averaged over electrodes) was compared with a two-sided Mann-Whitney U-test, and the result was used to define the directionality of a one-sided cluster-based permutation test (Fieldtrip, 2000 permutations). The latter was used to identify clusters of electrodes that, across tau-P patients, showed a greater level of relative gamma power than the tau-N ones. We repeated these analyzes also for the delta [1–3 Hz], theta [4–7 Hz], alpha [8–12 Hz] and beta [13–29 Hz] bands. Values of relative gamma power were then used for correlation analyses, using a Spearman or a Pearson Correlation Coefficient. For each group (tau-P: N = 7; tau-N: N = 9) we did the following analyses. 1) We investigated the relationship of average relative gamma power with the global tau-PET SUVR and the amyloid-PET centiloid (p-values are Bonferroni-corrected for the two comparisons). 2) For electrodes belonging to the significant cluster, we

Table 1
Patients' characteristics and summary. Summary of patient demographic and clinical data. Significant values are highlighted in bold. Summary results are reported as median values [inter-quartile range].

	Tau negative (N = 9)	Tau positive (N = 7)	p- value
Age, years	73 [70–76]	71 [69–72.5]	0.339
Gender (female), n (%)	1(11%)	7(100%)	0.002
Education, years	14 [11–16]	12 [11.5–16.5]	0.957
Clinical dementia rating scale	0.5 [0,1]	1 [0.75–1]	0.094
Mini mental state examination	27 [26–29]	23 [20–24]	0.014
Amyloid positivity, n (%)	1 (11%)	7 (100%)	0.002
2-s EEG epochs retained	281 [260–292]	265 [230–295]	0.758

correlated the local relative gamma power with the SUVR of the region of interest underlying the electrode placement, according to published guidelines (Okamoto et al., 2004). We excluded P9 and P10 as their projections are not described in Okamoto et al. and ran local correlations for the remaining 13 electrodes. For Fz, Cz and Pz, we used the average gamma power of each preponderant cortical area for each hemisphere (e.g. F3/F4 for Fz). The reported p-values are Bonferroni corrected for the number of electrodes tested.

3. Results

Of the 16 selected patients, 7 had a significant cortical tau deposition (i.e. tau-P), while 9 did not (i.e. tau-N). All tau-P patients also showed amyloid deposition on cerebral amyloid-PET, confirming the presence of AD pathology. Among tau-N patients, only one showed amyloid deposition on amyloid-PET. Demographic data and patients' characteristics are summarized in Table 1.

3.1. Gamma oscillations are increased in presence of cortical tau deposition, but not in the presence of amyloid

The average relative gamma power was higher in tau-P than in tau-N patients ($p = .042$, Fig. 1A). Correlation analyses revealed a strong positive correlation between the average gamma power and tau PET SUVR in tau-P patients ($\rho_{\text{Pearson}} = 0.88$, $p = 0.018$), but not in tau-N ($\rho_{\text{Spearman}} = 0.7$, $p = 0.087$, Fig. 1B). No significant correlation was found between the average relative gamma power and the global amyloid burden in neither group (not shown).

3.2. Gamma oscillations are increased in frontal and parietal electrodes

Tau-P patients showed higher gamma power than tau-N patients in frontal and parietal electrodes (Fp2, Fz, F3, F4, F7, Cz, C3, C4, Pz, P3, P4, P7, P8, P9, P10, $p = .009$, Fig. 1C). Moreover, in tau-P patients, a positive linear correlation between relative gamma power and local SUVR was found at the parietal electrodes ($\rho_{\text{Pearson}} = 0.93$, $p = 0.03$ and for P3; $\rho_{\text{Pearson}} = 0.95$, $p = 0.016$ for P4). No difference was found for the other frequency bands between tau-positive and tau-negative patients.

4. Discussion

EEG alterations have been observed in a large cohort of preclinical AD patients (Gaubert et al., 2019), advancing the hypothesis of complex compensatory mechanisms. Here, we found that gamma oscillations are increased in tau positive patients, while no difference between groups exists in other frequency bands. In tau-P patients, we also find a positive linear correlation between relative gamma power and global tau SUVR ($\rho = .88$, $p = .018$), while no correlation was found either in tau-N patients or with amyloid, suggesting a certain specificity of gamma oscillations with tau-related neurodegeneration. Interestingly, gamma oscillations also locally correlate with tau in parietal electrodes. These overlie the parietal and the precuneus cortices, which are known to show early tau-driven neurodegeneration in the course of AD (Frontzkowski et al., 2022). Tau protein accumulation is known to promote network hyperexcitability and in an AD murine model its reduction resulted in a decreased hyperexcitability, independently from the presence of A β 42 (Tok et al., 2022). Moreover, a recent study in AD patients found a positive linear correlation between the amplitude of TMS-evoked potentials at the level of the posterior parietal cortex and the levels of tau and p-tau in CSF (Casula et al., 2022). Hence, we hypothesize that the presence of tau protein and neurodegeneration could locally disrupt the physiological rhythms, forcing the remaining neurons to increase their activity to maintain the excitatory/inhibitory balance. Among the main limitations of this study, in addition to the small sample size due to its retrospective and exploratory nature, we acknowledge the

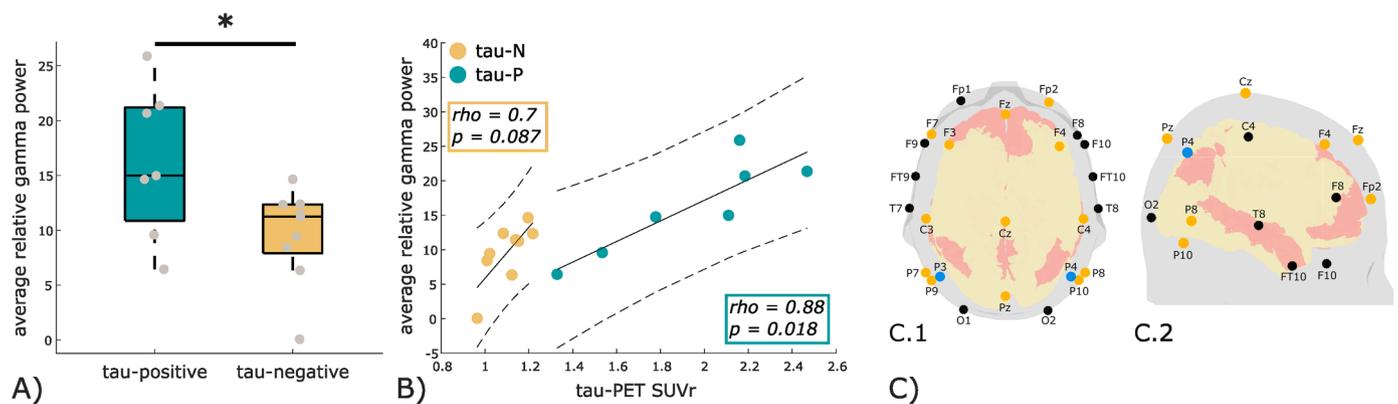


Fig. 1. Gamma power in tau-positive and tau-negative patients. A) Boxplot of the average relative gamma power (30–98 Hz) in tau-positive and tau-negative patients. The asterisk indicates statistical significance ($p < .05$). B) Scatterplot of Pearson correlation between the global tau-PET SUVR and the average gamma power in tau-P and tau-N patients. C.1) and C.2)) Maps of EEG electrodes (dots) plotted in axial (1) and right lateral sagittal (2) views of the scalp and brain. Yellow dots indicate electrodes that belong to the significant cluster ($p < .01$). Blue dots indicate the electrodes where local gamma power linearly correlated with local SUVR ($p < .05$). Pink areas are cortical regions belonging to the default mode network as previously described (Raichle, 2015) adapted to the scale 2 Lausanne parcellation scheme (Cammoun et al., 2012; Hagmann et al., 2008).

imbalance in sex between tau-P and tau-N, which might have biased some of the analyses, even though to our knowledge gamma oscillations are not known to be influenced by sex. The lower cognitive scores of tau-P patients on Mini Mental State Examination are in line with increased rate of neurodegeneration expected for these patients. In this view, further longitudinal studies in larger, balanced and age-matched cohorts employing high-density EEG will be crucial to determine the value of gamma oscillations to assess cortical tau deposition.

Funding and conflicts of interests

The Centre de la mémoire is funded by the following private donors under the supervision of the Private Foundation of Geneva University Hospitals: A.P.R.A. - Association Suisse pour la Recherche sur la Maladie d'Alzheimer, Genève; Fondation Segré, Genève; Race Against Dementia Foundation, London, UK; Fondation Child Care, Genève; Fondation Edmond J. Safra, Genève; Fondation Minkoff, Genève; Fondazione Agusta, Lugano; McCall Macbain Foundation, Canada; Nicole et René Keller, Genève; Fondation AETAS, Genève. The work of IR has been supported by the Swiss National Science Foundation (SNSF) Grant no. 192749 and CRSII5_209470 awarded to SV. MS and SV are scientific advisors and shareholders of Epilog NV, Ghent. MS was supported by the Swiss National Science Foundation project 180365. VG was supported by the Swiss National Science Foundation (projects 320030_169876, 320030_185028 and IZSEZ0_188355), by the Velux Foundation (project 1123), by the Schmidheiny Foundation, and by the Aetas Foundation. VG received financial support for research and/or speaker fees through her institution from Siemens Healthineers, GE Healthcare, Life Molecular Imaging, Cerveau Technologies, Novo Nordisk, Roche, Merck.

Object: verification statement

Dear Editors,

With this document, I hereby state that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

CRedit authorship contribution statement

Isotta Rigoni: Writing – review & editing, Writing – original draft,

Visualization, Validation, Software, Resources, Methodology, Formal analysis. **Umberto Nencha:** Writing – review & editing, Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Giovanni Battista Frisoni:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Serge Vuillemoz:** Writing – review & editing, Validation, Supervision, Funding acquisition. **Valetina Garibotto:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Margitta Seeck:** Writing – review & editing, Resources, Funding acquisition. **Daniele Altomare:** Writing – review & editing. **Federica Ribaldi:** Writing – review & editing, Validation, Supervision, Resources.

References

- Anon, 2021. Alzheimer's Disease Facts and Figures 17, 2021. <https://doi.org/10.1002/alz.12328>.
- Cammoun, Leila, Gigandet, Xavier, Meskaldji, Djalel, Thiran, Jean Philippe, Sporns, Olaf, Do, Kim Q., Maeder, Philippe, Meuli, Reto, Hagmann, Patric, 2012. Mapping the human connectome at multiple scales with diffusion spectrum MRI. *J. Neurosci. Methods* 203 (2), 386–397. <https://doi.org/10.1016/j.jneumeth.2011.09.031>.
- Casula, Elias P., Borghi, Ilaria, Maiella, Michele, Pellicciari, Maria C., Bonni, Sonia, Mencarelli, Lucia, Assogna, Martina, D'Acunto, Alessia, Di Lorenzo, Francesco, Spampinato, Danny A., Santarnecchi, Emiliano, Martorana, Alessandro, Koch, Giacomo, 2022. Regional precuneus cortical hyperexcitability in Alzheimer's disease patients. *Ann. Neurol.* 371–383. <https://doi.org/10.1002/ana.26514>.
- Digma, Leonardo A., Madsen, John R., Reas, Emilie T., Dale, Anders M., Brewer, James B., Banks, Sarah J., 2019. Tau and atrophy: domain-specific relationships with cognition. *Alzheimer's Res. Ther.* 11 (1), 1–12. <https://doi.org/10.1186/s13195-019-0518-8>.
- Fleisher, Adam S., Pontecorvo, Michael J., Devous, Michael D., Lu, Ming, Arora, Anupa K., Trucchio, Stephen P., Aldea, Patricia, Flitter, Matthew, Locascio, Tricia, Devine, Marybeth, Siderowf, Andrew, Beach, Thomas G., Montine, Thomas J., Serrano, Geidy E., Curtis, Craig, Perrin, Allison, Salloway, Stephen, Daniel, Misty, Wellman, Charles, Joshi, Abhinav D., Irwin, David J., Lowe, Val J., Seeley, William W., Ikonomic, Milos D., Masdeu, Joseph C., Kennedy, Ian, Harris, Thomas, Navitsky, Michael, Southekal, Sudeepti, Mintun, Mark A., 2020. Positron emission tomography imaging with [18F]Flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. *JAMA Neurol.* 77 (7), 829–839. <https://doi.org/10.1001/jamaneurol.2020.0528>.
- Frontzkowski, Lukas, Ewers, Michael, Brendel, Matthias, Biel, Davina, Ossenkopppele, Rik, Hager, Paul, Steward, Anna, Dewenter, Anna, Römer, Sebastian, Rubinski, Anna, Buerger, Katharina, Janowitz, Daniel, Binette, Alexa Pichet, Smith, Ruben, Strandberg, Olof, Carlgren, Niklas Mattsson, Dichgans, Martin, Hansson, Oskar, Franzmeier, Nicolai, 2022. Earlier Alzheimer's disease onset is associated with tau pathology in brain hub regions and facilitated tau spreading. *Nat. Commun.* 13 (1) <https://doi.org/10.1038/s41467-022-32592-7>.
- Gaubert, Sinead, Raimondo, Federico, Houot, Marion, Corsi, Marie Constance, Naccache, Lionel, Diego Sitt, Jacobo, Hermann, Bertrand, Oudiette, Delphine, Gagliardi, Geoffroy, Habert, Marie Odile, Dubois, Bruno, De Vico Fallani, Fabrizio, Bakardjian, Hovagim, Epelbaum, Stéphane, 2019a. EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease. *Brain* 142 (7), 2096–2112. <https://doi.org/10.1093/brain/awz150>.

- Hagmann, Patric, Cammoun, Leila, Gigandet, Xavier, Meuli, Reto, Honey, Christopher J., Wedeen, J. Van, Sporns, Olaf, 2008. Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6 (7), 1479–1493. <https://doi.org/10.1371/journal.pbio.0060159>.
- Mishra, Shruti, Brian, A. Gordon, Su, Yi, Christensen, Jon, Friedrichsen, Karl, Jackson, Kelley, Hornbeck, Russ, Balota, David A., Cairns, Nigel J., John, C. Morris, Ances, Beau M., Benzinger, Tammie L.S., 2017. AV-1451 PET imaging of tau pathology in preclinical Alzheimer disease: defining a summary measure. *NeuroImage* 161 (June), 171–178. <https://doi.org/10.1016/j.neuroimage.2017.07.050>.
- Okamoto, Masako, Dan, Haruka, Sakamoto, Kuniko, Takeo, Kazuhiro, Shimizu, Koji, Kohno, Satoru, Oda, Ichiro, Isobe, Seiichiro, Suzuki, Tateo, Kohyama, Kaoru, Dan, Ippeita, 2004. Three-Dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. *NeuroImage* 21 (1), 99–111. <https://doi.org/10.1016/j.neuroimage.2003.08.026>.
- Pontecorvo, Michael J., Devous, Michael D., Navitsky, Michael, Lu, Ming, Salloway, Stephen, Schaerf, Frederick W., Jennings, Danna, Arora, Anupa K., McGeehan, Anne, Lim, Nathaniel C., Xiong, Hui, Joshi, Abhinay D., Siderowf, Andrew, Mintun, Mark A., 2017. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain* 140 (3), 748–763. <https://doi.org/10.1093/brain/aww334>.
- Raichle, Marcus E., 2015. The brain's default mode network. *Annu. Rev. Neurosci.* 38, 433–447. <https://doi.org/10.1146/annurev-neuro-071013-014030>.
- Tok, Sean, Ahnaou, Abdallah, Drinkenburg, Wilhelmus, 2022. Functional neurophysiological biomarkers of early-stage Alzheimer's disease: a perspective of network hyperexcitability in disease progression. *J. Alzheimer's Dis.* 88 (3), 809–836. <https://doi.org/10.3233/JAD-210397>.
- Verret, Laure, Mann, Edward O., Hang, Giao B., Barth, Albert M.L., Cobos, Inma, Ho, Kaitlyn, Devidze, Nino, Masliah, Eliezer, Kreitzer, Anatol C., Mody, Istvan, Mucke, Lennart, Palop, Jorge J., 2012. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. *Cell* 149 (3), 708–721. <https://doi.org/10.1016/j.cell.2012.02.046>.
- Wang, Jing, Fang, Yuxing, Wang, Xiao, Yang, Huichao, Yu, Xin, Wang, Huali, 2017a. Enhanced gamma activity and cross-frequency interaction of resting-state electroencephalographic oscillations in patients with Alzheimer's disease. *Front. Aging Neurosci.* 9 (JUL), 1–7. <https://doi.org/10.3389/fnagi.2017.00243>.