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MEG Oscillatory Slowing in Cognitive Impairment is Associated with the Presence of Subjective Cognitive Decline

Ricardo Bruña[1,2], David López-Sanz[2,3], Fernando Maestú[4,5], Ann D. Cohen[6], Anto Bagic[7], Ted Huppert[8], Tae Kim[9], Rebecca E. Roush[10], Betz Snitz[10], and James T. Becker[10,11,12]

Abstract

The mechanisms behind Alzheimer's disease are not yet fully described, and changes in the electrophysiology of patients across the continuum of the disease could help to understand them. In this work, we study the power spectral distribution of a set of 129 individuals from the Connectomics of Brian Aging and Dementia project.

From this sample, we acquired task-free data, with eyes closed, and estimated the power spectral distribution in source space. We compared the spectral profiles of three groups of individuals: 70 healthy controls, 27 patients with amnestic MCI, and 32 individuals showing cognitive impairment without subjective complaints (IWOC).

The results showed a slowing of the brain activity in the aMCI patients, when compared to both the healthy controls and the IWOC individuals. These differences appeared both as a decrease in power for high frequency oscillations and an increase in power in alpha oscillations. The slowing of the spectrum was significant mainly in parietal and medial frontal areas.

We were able to validate the slowing of the brain activity in individuals with aMCI, appearing in our sample in areas related to the default mode network. However, this pattern did not appear in the IWOC individuals, suggesting that their condition is not part of the AD continuum. This work raises interesting questions about this group of individuals, and the underlying brain mechanisms behind their cognitive impairment.

Keywords

magnetoencephalography, Source reconstruction, Spectral power analysis, Cluster-based permutation test, Mild cognitive impairment

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Introduction

Although Alzheimer's disease (AD) is one of the most common causes of disability in older adults in developed countries[1] and the most common cause of dementia,[2] the mechanism behind the disease is still being identified. While the deposition of beta-amyloid plaques in the extracellular space and the formation of phosphorylated tau aggregates inside the neurons are considered evidence of the disease,[3] it is unknown whether they are its cause or a mere byproduct of the pathology. The fact that these deposits appear years before the first symptoms[4] indicates that Alzheimer's *disease* starts well before AD-*dementia*.

The prodromal stage of AD, usually termed amnestic mild cognitive impairment (aMCI),[5] has received broad attention during the last decades.[6] In this stage the brain activity is already impaired, but this situation might still be reversed[7]. Classical identification of aMCI patients is based on neuropsychological screening, and the aMCI due to AD classification requires some of the aforementioned AD-related biomarkers.[5]

[1]Electrical Engineering, Universidad de La Laguna, La Laguna, Tenerife, Spain
[2]Centro de Tecnología Biomédica, Universidad Politécnica de Madrid, Pozuelo de Alarcón, Madrid, Spain
[3]Psicobiología y Metodología en Ciencias del Comportamiento, Universidad Complutense de Madrid, Madrid, Madrid, Spain
[4]Experimental Psychology, Universidad Complutense de Madrid, Pozuelo de Alarcón, Madrid, Spain
[5]Center for Biomedical Technology, Universidad Politécnica de Madrid, Pozuelo de Alarcón, Madrid, Spain
[6]Neurosurgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[7]Neurology, University of Pittsburgh Medical Center Health System, Pittsburgh, Pennsylvania, USA
[8]Electrical Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[9]Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[10]Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[11]Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[12]Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Corresponding Author:
Ricardo Bruña, Radiology, Universidad Complutense de Madrid, Madrid, Spain.
Email: ricbruna@ucm.es

Recently, some neurophysiological markers also have been identified in aMCI patients[8]; specifically, the brain oscillations measured both using electro- (EEG)[9] and magnetoencephalography (MEG)[10] are presented by a decrease in the high-frequency oscillations (usually beta and gamma), accompanied by an increase in low-frequency oscillations (usually in the theta range).

Here we analyze MEG data from the NIH-funded Connectomics of Brain Aging and Dementia subproject of the Human Connectome Project (HCP). The study aims to undergo a multimodal assessment of the relationship of brain structure and function with healthy and pathological aging, with a special focus in the AD continuum.[11] The recruited sample consisted of older adults with and without cognitive impairment. During the recruiting stage we were able to identify an interesting subgroup of individuals who had cognitive impairment, according to the neuropsychological evaluation, but did not experience a subjective feeling of such an impairment. We termed this subgroup as impaired without complaints (IWOC) individuals.

The objectives of this work are twofold. First, we aim to validate whether our aMCI patients follow the aforementioned model, showing a slowing in the brain oscillations. Second, we aim to characterize the IWOC individuals according to this metric, in order to determine whether they show a typical aMCI profile. We hypothesize that the IWOC will show a brain activity similar to that of aMCI because their objective cognitive profiles were similar. Therefore, we anticipate that the lack of subjective cognitive decline in this population will not have a significant imprint in the spectral activity profile.

Materials and Methods

Participants

The sample used in this study was recruited at the University of Pittsburgh under the framework of the Connectomics of Brain Aging and Dementia project. From the 187 participants who provided task-free MEG data, we selected those who had a complete set of data (containing both MEG and T1-weighted MRI for source reconstruction). We also discarded those participants who had poor quality of signal (32, mostly due to magnetic noise due to dental implants), or those with incorrect positioning inside the MEG scanner (3). Last, we discarded those participants not falling into the three groups of interest of the study (10 individuals classified as non-amnestic MCI or AD and 12 participants who reported subjective cognitive decline but did not show cognitive impairment).

From the remaining sample we defined three groups: healthy older adults, comprised of 70 individuals (45 females and 25 males, age 66.0 ± 8.5, media $\pm$ standard deviation); amnestic MCI, with 27 individuals (20 females and 7 males, age 66.4 ± 10.4); and participants with cognitive impairment, but without subjective cognitive complaints, with 32 individuals (18 females and 14 males, age 60.2 ± 8.5). Table 1 shows a summary of the participants' demographic information.

Cognitive Evaluation

The participants were classified by the ADRC criteria[12] based on the results of a battery of neuropsychological tests that

Table 1. Demographic Description of the Sample Included in This Work.

	Control	IWOC	MCI	Statistical comparisons		
Sample size	69	32	27	HC IWOC	HC MCI	IWOC MCI
Age	66.0 ± 8.5	60.2 ± 8.5	66.4 ± 10.4	#	*n.s.*	‡
Sex (F/M)	45/25	18/14	20/7	*n.s.*	*n.s.*	*n.s.*
Race (A/B/W)	3/27/40	0/27/5	0/14/13	##	*n.s.*	‡
Education years	16.1 ± 2.9	13.0 ± 2.9	14.6 ± 2.6	##	•	‡
MoCA	26.6 ± 2.1	23.6 ± 2.9	22.7 ± 2.5	##	••	*n.s.*
PROMIS (abilities)	31.6 ± 6.1	33.1 ± 6.0	26.0 ± 7.5	##	*n.s.*	‡‡
PROMIS (concerns)	15.5 ± 6.5	12.4 ± 4.6	20.9 ± 7.4	#	•	‡‡
Word recall (delayed)	7.9 ± 1.5	5.6 ± 1.9	4.8 ± 1.7	##	••	n.s.
Rey figure (immediate)	18.6 ± 3.2	14.6 ± 4.2	14.3 ± 4.2	##	••	n.s.
BNT (spontaneous)	28.1 ± 2.1	25.5 ± 2.9	24.9 ± 3.4	##	••	n.s.
TMT B (time)	62.8 ± 23.4	90.9 ± 50.2	96.8 ± 40.5	##	••	n.s.

F/M Stands for Females/Males. A/B/W Stands for Asians/Blacks/Whites. MoCA Stands for Scores According to the Montreal Cognitive Assessment. PROMIS Stands for Patient-Reported Outcomes Measurement Information System. TMT Stands for Trail Making Test. All Scores (Excluding sex and Race) are Provided as Mean $\pm$ Standard Deviation. Statistical Comparisons are Based on a Pairwise Independent Samples t-Test (age, Education Years and Neuropsychological Tests) or a Pairwise Fisher's Exact Test (sex and Race). The Significance Levels are Described as Follow: #: Significant Difference ($p < 0.05$) for the Comparison Between Control and IWOC Groups; ##: Significant Difference ($p < 0.001$) for the Comparison Between Control and IWOC Groups; •: Significant Difference ($p < 0.05$) for the Comparison Between Control and MCI Groups; ••: Significant Difference ($p < 0.001$) for the Comparison Between Control and MCI Groups; ‡: Significant Difference ($p < 0.05$) for the Comparison Between IWOC and MCI Groups; ‡‡: Significant Difference ($p < 0.001$) for the Comparison Between IWOC and MCI Groups; *n.s.*: non-Significant for the Corresponding Comparison.

included: global cognitive status measured with the Montreal cognitive assessment (MoCA)[13]; confrontation naming measured with the Boston Naming Test[14]; verbal free recall measured with the CERAD word list memory test[15,16]; planning measured with the Trail Making Test A and B[17]; and visuospatial construction and visual memory measured with a 24-point modified Rey-Osterreith complex figure.[18] Participant's classification was made independently by JTB and BES, and any differences were resolved in a group discussion.

Participants also completed individual tests and questionnaires including items from the NIH Toolbox,[19] the PROMIS applied cognition scales,[20] and several paper and pencil questionnaires (a brief summary of some relevant measurements are shown in Table 1) covering symptomatology, personality, diet, and exercise.

Brain Imaging Data

We acquired functional brain imaging data using a whole-head Elekta Neuromag MEG system with 306 independent channels (102 magnetometers and 204 planar gradiometers) located inside a magnetically shielded room in the UPMC Brain Mapping Center (Pittsburgh, PA). Before data acquisition, we prepared the participants by placing two sets of bipolar electrodes around their eyes, aimed to capture eye movements and blinks, and another pair of bipolar electrodes across their chest, in order to capture heart-related activity. We also placed 4 head position indication (HPI) coils on the head of the participants, to allow for continuous on-line head position monitoring. Finally, we recorded the position of three anatomical landmarks (nasion and both preauricular points) and the four HPI coils, together with around 100 points distributed across the head surface, using an FASTRAK 3D digitizer (Polhemus, Inc., Colchester VT).

We recorded a minimum of 5 minutes of task-free (resting state) data from each participant while having their eyes closed, using a sampling rate of 1000 Hz and an anti-alias filter between 0.1 and 330 Hz. After acquisition, we used the temporal extension of the signal space separation (tSSS) algorithm,[21] as provided by MaxFilter 2.2 software, to remove external noise and compensate for head movements during the recording (window length of 10 s, correlation limit of 0.90). We removed ocular and cardiac activity, together with identified noises using independent component analysis by means of SOBI,[22] and marked the remaining artifacts using FieldTrip toolbox.[23] The resulting clean data were organized in non-overlapping epochs of 4 seconds of artifact free brain activity, resulting between 120 and 240 epochs per participant. The final number of trials did not differ between groups. Finally, as MEG data is highly redundant after tSSS,[24] we discarded the data from the gradiometers and continued the analysis using only that from the 102 magnetometers.

Source Reconstruction

We analyzed MEG data in source space using the individual anatomical information of the patient to build the conduction model. For that, we used the T1-weighted MRI from each participant, and segmented this image into the different tissues in the head (gray and white matter, cerebrospinal fluid, soft tissue, and bone) using the unified segmentation algorithm[25] as provided in SPM12.[26] From this segmented volume we created two surfaces: one from the union of the white matter, gray matter, and cerebrospinal fluid, namely the brain of the participant, and defining the inner skull cavity; and other defining the scalp of the participant. The scalp surface was used, in conjunction with the head shape digitized for MEG acquisition, to realign the MRI into the coordinate system of the MEG scan. The inner skull surface was used to build a realistic conducting head model using a single shell and a modified spherical solution.[27]

We defined a homogenous source model in MNI space, using a three-dimensional grid with 1 cm of spacing. The sources were labeled according to the Automated Anatomical Labelling,[28] and only those source positions falling into a cortical region were retained, resulting in a source model of 1210 source positions. This head model was linearly transformed into the participant's MRI space using SPM12, and then into MEG space. Finally, we combined the source model, the head model, and the sensor positions and orientations to solve the forward problem and generate a lead field representing the forward model.

For the inverse model we used a spatial filter approach based on linearly constrained, minimum variance beamformers.[29] For that, we used the trial-averaged covariance matrix of the data filtered between 2 and 45 Hz, and a Tikhonov regularization with 5% of the average sensor power. These parameters where selected to try and mimic previous analyses by the group.[30–32]

Spectral Analysis

We calculated the characteristic spectra in source space using an average periodogram approach. First, for each source position, we calculated the Fourier transform of the data, separately for each of the three dipole orientations, for each 4-second epoch, and using a discrete prolate spheroidal sequence taper with 0.5 Hz smoothing, as implemented in FieldTrip toolbox. Then, we calculated the epoch spectra by taking the absolute value of each tapered spectra and averaging them. Last, we normalized the spectrum for each position by the total spectral power between 2 and 45 Hz, obtaining the relative spectral power distribution for each source position and participant.

Statistical Analysis

In order to minimize the constraints introduced into the data, the statistical analyses were based on a nonparametric cluster-based permutation test (CBPT).[33] We performed a separate statistical test for each source position and frequency bin, and clustered the significant results using spatial and frequency contiguity. Then, the results are corrected simultaneously for multiple comparisons and violations of normality by comparing the cluster with a set of random partitions of the data. The clusters resulting

from this analysis can appear in any frequency and brain region and are guaranteed to be statistically significant.

We based the statistical analyses in an ANOVA contrast. When required, the post-hoc analyses were performed using Tukey's honestly significant difference (HSD) test over the elements (source positions and frequencies) pertaining to the significant cluster.

Results

Broadband Exploration

The first comparison was completely model-free, contrasting the relative power distribution of the three groups. The analysis was performed separately for each of the 1210 source positions and each frequency bin, and then corrected for both multiple comparisons and violations of normality using a CBPT. The results, depicted in Supplementary Figure 1, show a large significant cluster ($p = 0.0275$) covering the frequency range between 15 and 45 Hz, and a large portion of the brain, mainly parietal, medial frontal, and right temporal areas.

The post-hoc analyses in this cluster showed that the aMCI group was different both from the Control group and, more interestingly, the IWOC group. The comparison between the Control and IWOC groups found that only 2% of the members of the cluster (this is, combinations of source position and frequency bins) were significant, which is well within what would be expected by chance. The comparison between the Control group and the aMCI group showed that 52% of the members of the cluster showed a significantly lower power in the aMCI individuals, with a spatial distribution depicted in Figure 1a and comprising mainly parietal and right temporal areas. Last, the comparison between the IWOC and aMCI groups showed that 66% of the members of the cluster showed significantly lower power in the aMCI group, with a distribution similar to that of the previous comparison and depicted in Figure 1b and mainly comprising medial frontal and right temporal areas. Given the large range of frequencies spanned by the cluster, we provide a more detailed description of its spatial distribution at different frequencies in Supplementary Figure 2. In summary, aMCI individuals show significantly overall lower relative power in high beta and gamma bands when compared to both healthy older adults and IWOC individuals.

The individuals in the IWOC group were significantly younger than those in the rest of the groups, so we then analyzed the effect of age on our results. We found no correlation between age and the power each band band ($p > 0.1$), and when age was introduced into an ANCOVA model with group, the age was unrelated to power ($p > 0.1$), while the effect of group remained significant ($p = 0.0030$).

Alpha Band Exploration

Following several previous studies in patients with aMCI [9] we decided to complete the description of our sample by analyzing the total relative power in the alpha band. For that, we calculated the total relative power between 8 and 12 Hz and performed an analysis similar to that described above, but considering only spatial contiguity. The results are shown in Supplementary Figure 3 and show a significant cluster ($p = 0.0258$) covering parietal and frontal regions.

The post-hoc analysis of this cluster showed that the aMCI individuals were different from both the healthy controls and the IWOC individuals. The comparison between healthy older adults and IWOC individuals found no significant differences between these groups. The comparison between the Control and aMCI groups showed a higher relative alpha power in the aMCI group in the regions depicted in Figure 2a, mainly parietal and medial frontal areas. Last, the comparison between the IWOC and aMCI groups showed a higher relative alpha power in the aMCI individuals, in regions similar to those found in the previous comparison, as can be observed in Figure 2b. In summary, the aMCI individuals show a higher relative alpha power in parietal and frontal areas when compared to both healthy older adults and IWOC individuals.

Similarly to the previous analysis, we tested the effect of age on our results. Again, we found no correlation between age and the power in alpha band ($p > 0.1$), and age was not a significant factor in the ANCOVA model ($p > 0.1$), while the effect of group remained significant ($p = 0.0162$).

Discussion

The purpose of this study was to evaluate the power spectrum distribution of individuals recruited from within the Connectomics of Brain Aging and Dementia project who were at different stages of the AD-continuum. First, we wanted to validate the slowing of the spectrum phenomenon (ie, shifting towards the left) in aMCI individuals, when compared to healthy older adults. Secondly, we wanted to evaluate the spectral characteristics of the individuals showing objective cognitive impairment in the absence of subjective complaints in order to fit these individuals into the AD biomarker continuum.

Comparison of Healthy Older Adults and aMCI Patients

Regarding the comparison between healthy older adults and aMCI patients, we were able to successfully replicate the slowing of the spectrum found in previous works in patients in the dementia continuum.[34,35] Nevertheless, in contrast to the literature our results showed that the power shifted from high beta and gamma bands towards the alpha band, and not the theta band, as usually reported.[9,10] However, it is important to note that our sample, while fulfilling the criteria for aMCI, was younger, with an average age of 66 years, than is usually reported in studies of this kind (ie, 70 years old). The healthy aging process has also been described in terms of power spectral density as a process of slowing of brain oscillations,[36] and therefore the younger age of our sample could be the reason to this discrepancy.

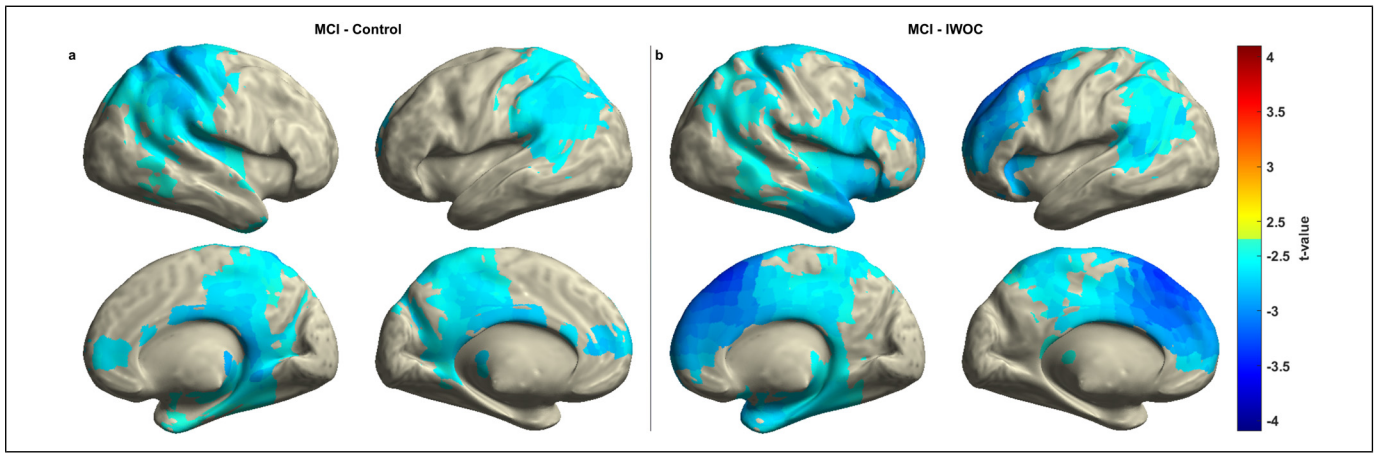

Figure 1. Significant results for the pairwise comparisons in relative power taking into account only the cluster obtained for the ANOVA comparison. a) Results for the comparisons between healthy older adults and MCI patients. b) Results for the comparison between IWOC individuals and MCI patients. The color represents the average t-value, for each source position, in all the significant frequency bins pertaining to the cluster. In both cases red colors indicate higher relative power levels in the MCI patients, and blue colors indicate lower relative power levels in the MCI patients. The results are corrected using Tukey's honestly significant difference. The figure only shows those source positions significant for at least 20% of the frequencies in the cluster (15 to 45 Hz).

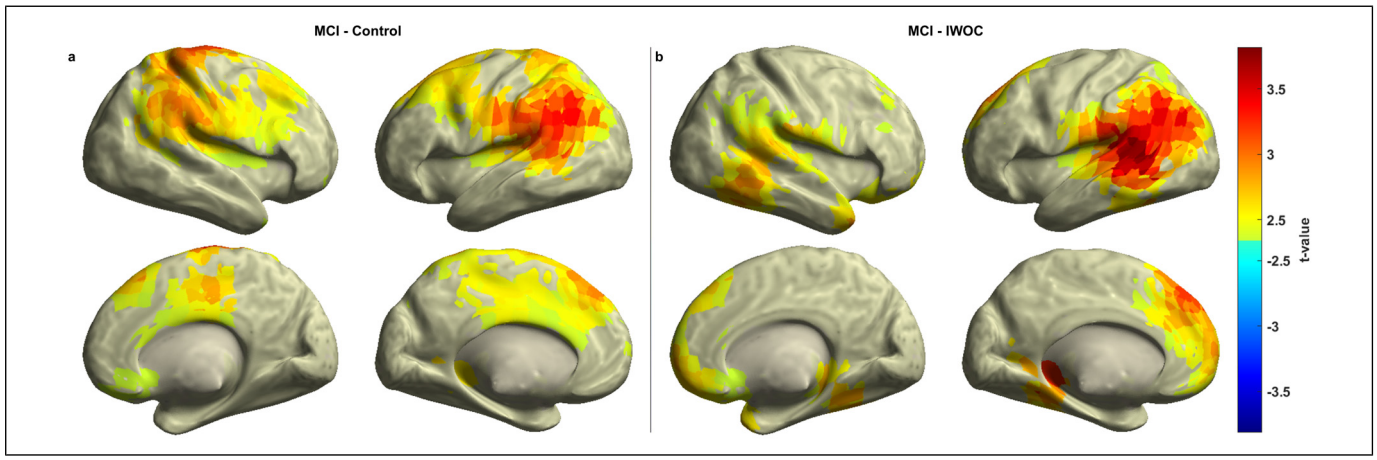

Figure 2. Significant results found in the pairwise comparisons in relative alpha power taking into account only the cluster obtained for the ANOVA. a) Results for the comparisons between healthy older adults and MCI patients. b) Results for the comparison between IWOC individuals and MCI patients. The color represents the t-value for each significant source position. In both cases red colors indicate higher relative alpha power levels in the MCI patients, and blue colors indicate lower relative alpha power levels in the MCI patients. The results are corrected using Tukey's honestly significant difference.

The differences between healthy older adults and aMCI patients were distributed across all the brain regions but were most prominent in the posterior cingulate, bilateral parietal cortices, and anterior cingulate. These areas have been extensively described as part of the default mode network,[37] a set of brain areas whose functional connectivity has been found to be reduced in MCI and AD patients.[38] This reduction of functional connectivity has been largely described using functional MRI and has given rise to the hypothesis of disconnection in AD.[39] Interestingly, functional connectivity, as measured with functional MRI, is closely linked to the beta band.[40] In his work, O'Neill and colleagues made use of amplitude envelope correlations, a connectivity metric tightly linked to power spectral density modulations, which could make our findings (power decrease in high beta band) consistent with theirs. However, the current study focuses on the distribution of power across the frequency spectrum, and inferring functional connectivity effects from them could be somewhat tenuous and should therefore be treated as a tentative interpretation. Interestingly, our findings involve several regions, such as the cingulate cortex and the hippocampus, connected by the diagonal band of Broca, a set of fibers known to be mainly formed by

cholinergic neurons.[41,42] Previous studies have reported a significant deterioration of this tissue even in the earliest stages of the disease,[43] which would argue in favor of the interpretation of our findings in relation to early AD pathology.

This slowing effect was evident both in the reduction of the high-frequency and the increase in lower frequencies power (ie, alpha range), supporting the idea of a shifting towards the left in brain oscillations. Nevertheless, it is important to remember that, when using relative power, the frequency bands are not independent, and an increase in the power of one band must be accompanied by a decrease in power in another one. With this in mind, the results could be equally explained by an overall slowing of the brain activity, a single decrease in high-frequency oscillations, or a single increase in alpha oscillations. As all three scenarios draw a picture where the balance of high and low frequency oscillations shifts towards the slow oscillations, we favor the use of "slowing" to describe the phenomenon in agreement with previous literature.[44–47]

Characterization of the IWOC Population

In contrast to the previous comparison, the results found when trying to characterize the IWOC population in the AD continuum did not conform to what we initially hypothesized. While controls and aMCI patients showed differences similar to those already reported in the literature, the IWOC individuals were virtually indistinguishable from the healthy older adults, and significantly different from the aMCI patients. This forces us to reject our original hypothesis, this is, that the IWOC individuals are just aMCI patients without a subjective feeling of cognitive decline. In fact, our results suggest that these individuals are not part of the AD continuum, at least when considering their power spectral density alone, which is a well-known neurophysiological hallmark alteration of early AD.[48] Other AD-related alterations could present in these individuals, but its exploration escapes the scope of this work.

However, some considerations must be taken into account. First, a recent paper using this cohort[11] reported that the IWOC group had a near absence of Aβ accumulation. Even though participants in both studies were part of the same group their exact composition were not identical. Thus, we cannot rule out that IWOC participants were not on the AD pathology spectrum, and that with their younger age, the amyloid cascade was not yet well developed.

Second, the racial profile of the IWOC individuals is unbalanced when compared to the other two groups. Moreover, and considering their age range, it is likely to assume that these participants are mainly direct descendants from a generation of black people migrating from the rural USA environments to northern cities around the 1950s and 60s. Racism is a social and not biological construct that affects the positive (eg, education, access to health care) and negative social determinants of health (eg, poverty, social isolation) may result in a different structural and functional brain integrity.

In summary, the similarity between the IWOC individuals and the healthy older adults and the pattern of difference between this group and the aMCI patients could be drawing several different scenarios. One possibility is that the IWOC individuals are cognitively healthy individuals with naturally occurring low neuropsychological scores. This possibility is supported by the fact that their perceived cognitive status is normal, with subjective ratings even above those of the healthy older adults, both in their subjective cognitive perceived decline and abilities. In this case, the diagnosis procedure would be misclassifying as impaired a cognitively normal individual. A second interpretation of our findings would be that the cognitive impairment exists not as part of the AD continuum, but as part of a completely different disease. In this case, the lack of subjective cognitive deterioration could be a symptom of the disease and should be used to avoid misdiagnoses. The presence of subjective cognitive deterioration in MCI is a topic that been debated for a long time in AD literature, giving rise to numerous and polarized positions. Views range from those arguing that it should be considered a mandatory criterion to establish an aMCI diagnosis,[49] to that putting up that this subjective manifestation may result unnecessary, or even misleading, when taken into consideration for the diagnosis.[50] Our results seem to support the former interpretation, at least from an electrophysiological perspective, since IWOC did not show the typical spectral alterations that have been described for a long period of time both in AD and preclinical stages.

Limitations of This Work

While the results of this work are statistically sound, some issues must be pointed out. Firstly, the sample size is similar to that of other MEG studies, but might be insufficient to notice subtle effects, as could be the case of those existing between healthy controls and IWOC individuals. In addition, the sample size is unbalanced, and this is known to be a problem when using Tukey's HSD correction. We decided to use all the individuals in our sample to maximize the statistical power of the work, but future efforts should be made to address it and to achieve homogeneous sample sizes for all the groups of interest. Also considering sample size, the reduced number of participants without cognitive impairment but manifesting subjective complaints recruited in this study did not allow us to include this interesting group in the comparison. Last, we cannot guarantee that the aforementioned racial bias does not make a contribution to our results, since racial influence on AD has been largely ignored in the literature. There is a clear disproportion of black participants in the IWOC sample compared to both the healthy controls and the aMCI patients. Future works should explicitly address racial contribution in this field in order to correctly and homogeneously represent the population. Nevertheless, this can prove challenging; the later report addressing the issue[51] has shown that, even when researchers actively look for unbiased samples, black

individuals are less likely to participate in scientific research than white individuals, mainly due to doubts about being treated fairly (22%, for 3% in white individuals) or due to general distrust in medical research (24%, for 10% in white individuals). A positive action must be taken to bring scientific research closer to minorities, maybe through science communication programs addressed to these population.

Conclusions

We were able to replicate the largely described slowing of the brain oscillations in the aMCI sample recruited in the framework of the Connectomics of Brain Ageing and Dementia project. Nevertheless, when we tried to evaluate the spectral profile of the IWOC individuals using the same approach we failed to find any difference between the power spectral distribution of this group when compared with the controls. Moreover, the IWOC group was significantly different from the aMCI group in regions very close to those found in the comparison between aMCI patients and healthy controls. Two reasons could explain these findings: firstly, the IWOC individuals could be a population outside of the AD continuum, and their impairment could have a completely different origin; secondly, the characteristic MCI profile found in the majority of the studies could be specific to the MCI patients with subjective complaints, and therefore fails in these individuals. This dichotomy can only be solved by a careful follow up of the IWOC individuals in order to monitor if they evolve inside the AD continuum or follow a different trajectory.

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Author Contributions

FM, ADC, AB and JTB worked on the conception and design of the work. RR, BS and JTB acquired the data. RB, DL-S, KT and BS analyzed the data. All authors worked on the interpretation of the data and the writing of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Supplemental material

Supplemental material for this article is available online.

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