



Does engagement in cognitive activities contribute to the preservation of brain structure and connectivity in older adults?

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ARTICLE INFO

Keywords:

Aging
Cognitively active
Cognitive impairment
Functional connectivity
Neuropsychological assessment
Structural connectivity

ABSTRACT

Aging is associated with changes in brain structure and connectivity and decrements in certain cognitive abilities. The benefits of active lifestyles in the aging brain and cognition in older adults have been widely described. This work aimed to explore the associations between brain parameters and cognitive performance in a sample of cognitively active adults who participate in University Programs for Seniors (UPS).

Method: forty cognitively active adults aged 55 or older underwent a neuropsychological battery and structural magnetic resonance imaging data (MRI), diffusion tensor imaging (DTI) and functional imaging at rest (fMRI). Composite scores for four cognitive domains were calculated and the sample was then divided into two groups: a group with no low scores and a group with one or more low scores across cognitive domains.

Results: the results show no association between brain volume and the risk of presenting low scores, and also an absence of association between brain volume, white matter integrity, functional connectivity and cognitive performance.

Conclusions: Active older adults might not follow the expected brain and cognitive age-changes expected in the general population. Participation in cognitive stimulating activities might then be a possible factor for brain maintenance and determinant for increasing the cognitive reserve and cognitive impairment resistance during aging.

1. Introduction

The global population is aging at an unprecedented rate, with projections indicating that by 2050, older adults will comprise over 30 % of the population in countries such as Spain [1]. This demographic shift is accompanied by a rising incidence of neurodegenerative diseases, including Mild Cognitive Impairment (MCI) and dementia, as advanced age remains the primary risk factor [2,3]. Given the current absence of effective treatments to halt cognitive decline [4,5,6,7], research has increasingly focused on identifying factors associated with successful aging that may serve as protective elements in mitigating neurodegenerative processes.

In this regard, studying the brain's structural and functional

architecture in healthy aging is essential. Advanced neuroimaging techniques have facilitated the differentiation between normal age-related brain changes and pathological deterioration [8]. Structural connectivity, assessed through Diffusion Tensor Imaging (DTI), and functional connectivity, analyzed via resting-state functional Magnetic Resonance Imaging (rs-fMRI), have provided insights into neural reorganization processes that support cognitive function in older adults [9,10].

Since aging is a heterogeneous process, various modifiable factors, including education, physical activity, and social engagement, have been identified as key contributors to brain health [11,12,13]. Active aging, particularly through participation in lifelong learning programs, has been linked to greater cognitive reserve and enhanced brain

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<https://doi.org/10.1016/j.jns.2025.123658>

Received 30 April 2025; Received in revised form 30 July 2025; Accepted 12 August 2025

Available online 13 August 2025

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connectivity [14,15,16]. However, research on cognitively active older adults remains limited.

This study examines brain structure and connectivity in older adults enrolled in university programs for seniors, investigating their relationship with cognitive performance. Understanding how an active lifestyle influences brain integrity and function could offer valuable insights for developing preventive strategies to promote healthy aging and delay cognitive decline [17].

2. Methods

2.1. Participants

This was a cross-sectional observational study with cognitively healthy and active individuals living independently in the community. The sample included 40 participants over 55 years of age from the Neuroprevent project at the Miguel Hernández University (UMH, <https://sabiex.umh.es>). This project aims to identify cognitive factors and brain structures that protect against cognitive deterioration and is part of the University Program for Seniors at the UMH (SABIEX, SABiduría Y EXperiencia), a comprehensive program that promotes healthy and active aging and offers academic courses with relevant topics (politics, sociology, economics, physiology, art, etc.). Additionally, it offers the opportunity to participate in different collective-recreational activities, such as sport, seminars, radio programs, magazine and theater and film workshops. This diversity of activities and educational environment allows the participants to enrich their knowledge and keep them cognitively active and stimulated in their daily lives.

Participants who voluntarily agreed to take part in the study were included if they were 55 years or older, classified as cognitively normal (Mini-Mental State Examination [MMSE] > 23) [18], reported no subjective cognitive complaints during a semi-structured interview (Clinical Dementia Rating Scale [CDR] = 0) [19], and were independent in activities of daily living (Instrumental Activities of Daily Living Scale [IADL] ≥ 7) [20]. Potential participants were excluded if they refused to participate in the neuropsychological assessment or the MRI study, if they had vision and/or hearing impairments that precluded the administration of cognitive tests or presence of corporal paramagnetic body devices that could impede and MRI study. To ensure the representativeness of the sample concerning the general population, medical history was not considered as an exclusion (e.g., diabetes, high blood pressure, cancer, psychiatric disorders, metabolic disease). This was deemed appropriate as comorbidities are frequent with aging [21], and because cognitive normalcy was mandatory to be included in the study. Thus, including only participants with no medical history would render the sample unrepresentative of the population compromising the external validity of the results.

2.2. Procedure

2.2.1. Neuropsychological assessment

All participants were assessed individually by a board-certified clinical neuropsychologist and trained undergraduate or master's degree students. Participants provided data regarding socio-demographics and personal and familial medical history, signed the informed consent and underwent a comprehensive neuropsychological assessment covering a range of cognitive functions. The tests included have been previously reported [22,23,24] and included measures of attention, working memory, information processing speed, verbal and visual memory, visuospatial abilities, executive functioning, and language. The Geriatric Depression Scale (GDS) was used to assess depressive symptoms [25,26]. This work was performed according to the Declaration of Helsinki and all participants provided informed consent prior to enrollment. This project was approved by the UMH Ethics Committee (DPS.JOC.01.21) and was funded by the Conselleria d'Innovació, Universitats, Ciència i Societat Digital, Generalitat Valenciana

(NEUROPREVENT project, GV/2021/139).

2.2.2. Neuroimaging

2.2.2.1. Image acquisition. All participants MRI acquisition study in a 1.5 Tesla scanner Signa Explorer, equipped with a 16-channel matrix head coil. All participants' MRI images were acquired in the same scanner. Participants were placed into the scanner and were instructed to relax and not to think of anything without falling asleep while images were taken, and level of spontaneous brain activity was measured. Three classes of brain images were acquired:

- Anatomical images: High resolution T1 images were acquired with a BRAVO sequence with 3D magnetization and the following parameters: repetition time (RT) = 2.300 ms, echo time (TE) = 5.0 ms, voxel size = $1 \times 1 \times 1.1 \text{ mm}^3$, slice thickness = 1.1 mm, field of view (FOV) = $256 \times 256 \text{ mm}^2$, 170 contiguous sagittal slices covering the entire brain and brainstem.
- Resting state functional images: T2* functional data were acquired with a gradient echo-planar imaging sequence over a 10 min session using the following parameters: 200 whole-brain volumes with TR/TE = 3000/30 ms, flip angle = 90, inter-slice gap = 0 mm, voxel size = $3 \times 3 \times 3 \text{ mm}^3$, 80×80 matrix, slice thickness = 3 mm, 170 oblique axial slices, interleaved in descending order.

Diffusion images were acquired with a single shot spin-echo echo-planar imaging (SE-EPI) images with the following parameters: TR = 13.000 ms, TE = 85 ms and 50 ms, voxel size = $2.5 \times 2.5 \times 2.5 \text{ mm}^3$, slice thickness = 2.5 mm, FOV = $240 \times 240 \text{ mm}^2$, for each image, 170 contiguous sagittal slices were acquired covering the entire brain and brainstem. A total number of 64 volumes were acquired corresponding to different gradient directions with $b = 1000 \text{ s/mm}^2$. One extra 3D diffusion image was acquired for $b = 0 \text{ s/mm}^2$, needed for the diffusion imaging preprocessing.

2.2.2.2. Image processing and brain connectivity analysis

2.2.2.2.1. T1 anatomical images. The preprocessing of T1 anatomical images primarily involves aligning each subject's image with the anterior commissure-posterior commissure (AC-PC) line, applying scanner bias field correction, and performing skull stripping of the brain image. The preprocessing pipeline involved brain extraction to remove non-brain tissue, tissue segmentation into GM, white matter (WM), and cerebrospinal fluid (CSF), and non-linear registration to align individual GM maps to a common template in MNI space. GM values were modulated to account for volumetric changes caused by registration, followed by Gaussian smoothing with a 3 mm sigma to reduce noise and enhance group difference detection. Statistical analysis was performed using Randomise for voxel-wise non-parametric permutation testing, with multiple comparisons corrected through threshold-free cluster enhancements (TFCE). For a detailed description of the pipeline used see reference [27]. Subcortical volumetric analysis was performed from the pre-processed brain image, the FIRST tool from the FSL toolbox (v6.0.1) was applied to segment the subcortical regions defined in the Desikan-Killiany Brain Atlas [28]. The result is the volume in mm^3 of the following structures: thalamus, caudate nucleus, putamen, pallidum, brainstem plus fourth ventricle, hippocampus, amygdala, and nucleus accumbens. Cortical thickness analysis was estimated in millimeters in regions included in the Desikan-Killiany Brain Atlas using the FreeSurfer toolbox (v6.0.0). Specific regions were caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, parahippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, pericalcarine, post central, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal,

superior temporal, supramarginal, frontal pole, temporal pole, transverse temporal and insula. The tool yielded cortical thickness values for both the left and right hemispheres, but an average cortical thickness between the left and right hemispheres was calculated.

2.2.2.3. Diffusion imaging and structural connectivity. For the preprocessing, T1 anatomical and diffusion images were employed, using the Rtrix3 (v3.0_RC3), FSL (v6.0.1), and ANTs (v2.3.1) tools. After that, we removed noise and correct for distortion caused by eddy currents. Using the distortion-corrected images, a diffusion tensor for each voxel was fitted and the values of FA and MD were calculated. For further details, see [27]. A higher (lower) value of FA (MD) indicates greater (lower) integrity of the tract. Values of FA = 0 indicate that the diffusion follows equally the three eigenvector directions of the diffusion tensor (ie. Does not follow any specific direction), while values of FA = 1 indicate fully diffusion in only one eigenvector direction. Similar to previous work [29], we choose the following tracts for assessing specific FA and MD values, using the JHU White-Matter Tractography atlas provided within the FSL6 package was used [30]. In particular, the tracts included were anterior thalamic radiation, corticospinal tract, cingulum (cingulate gyrus), cingulum (hippocampus), forceps major, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus, and the superior longitudinal fasciculus (temporal part).

2.2.2.4. T2* functional images and functional connectivity at rest. The preprocessing of resting state functional MRI was carried out combining functions from the FSL (v6.0.1) and AFNI (v23.0.04). After correction for EPI (Echo-Planar-Imaging) gradient distortion, slice timing correction was applied. Next, each volume was aligned with the central volume to correct possible head motion artifacts using MCFLIRT (incorporated in FSL). Next, intensity normalization was performed and linear regression was applied to remove confounding factors such as motion time series, linear and quadratic trends, average cerebrospinal fluid (CSF) signal, and the average WM signal. Additionally, a bandpass filter between 0.01 and 0.08 Hz was applied. To correct for potential artifacts, we implemented “scrubbing”, interpolating temporal points with frame-wise displacements >0.5 or DVARS >0.5 % using cubic spline interpolation [31]. After preprocessing, functional data were spatially normalized to the MNI152 standard template with a voxel size of $3 \times 3 \times 3 \text{ mm}^3$. Finally, all voxels were spatially smoothed with a full-width at half-maximum (FWHM) of 6 mm using an isotropic Gaussian kernel. The details of the entire process are available at Jimenez-Marin et al. [27]. For getting the different Resting State Networks (RSN) components, the MELODIC tool from the FSL (v6.0.1) was employed. The amount of activation for each functional network and subject was calculated as the overlapping with RSN templates at population-level [32], thresholding each component to absolute Z values of 3. Subsequently, cerebral maps for each subject at the voxel level was computed. This resulted in the activation value of the following functional networks: Medial Visual, Occipital Pole Visual, Lateral Visual, Default Mode Network, Cerebellum, Sensorimotor, Auditory, Executive Control and Frontoparietal.

2.3. Statistical analysis

The statistical package SPSS v.26 (IBM; Armonk, NY, USA) and JAMOVI 2.6.19 were used for analyses. Statistical significance was set at 0.05. Independent samples *t*-tests were carried out to determine whether there were significant sex differences in demographic characteristics, MMSE, IADL, and GSD.

2.3.1. Neuropsychological data

To interpret performance on neuropsychological tests, raw scores were converted to z-scores using normative data for cognitively active

Spanish adults [22,23,24]. The tests included in the neuropsychological battery were divided into four cognitive domains (composites) following composites employed in previous research for group comparison. The selection of tests included in each composite was realized following Jak/Bondi actual criteria for MCI diagnose [33]. Tests included in each cognitive domain are provided in Table 1.

Each composite was calculated following the weighted z-method or ‘Stouffer’s method,’ that allows for combining information across multiple tests [34]. Each composite is calculated by the sum of the z-scores of the tests based on the means and standard deviation and then divided by the square root of the number of tests included in each composite. The composite for each cognitive domain was labelled as low score when the weighted z-score was equal to or lower than -1.5 . The sample was then divided into two groups: a group with no low scores and a group with one or more low scores across cognitive domains. Although we are aware that the number of expected low scores increases as the number of measures in the battery increases [35], we selected only one low score as a grouping factor for two main reasons: first, the probability of having a low composite score is lower than the probability of having low scores on each of the measures included in the composite score, and second, because using only one composite low score provided a more balanced sample sizes for MRI comparisons. Binary logistic regression was then performed to analyze the association between total brain volume, left and right hemisphere volume and the risk of presenting at least one composite low score.

2.3.2. Brain morphometry

T1-weighted MRI images group comparison was performed between two different groups: Group 1 included 21 subjects with at least one low score, while Group 0 included 19 subjects with no low scores. The analysis aimed to investigate local grey matter (GM) differences between the groups using voxel level brain morphology. Multiple voxel-level comparison correction was addressed with the non-parametric cluster statistics threshold-free cluster enhancement (TFCE).

2.3.3. Brain connectivity

The objective was to investigate differences in functional connectivity or spatial patterns between groups (21 subjects with at least one low score and 17 subjects with no low scores) using dual regression based on ICA-derived networks [36]. The pipeline began with Group ICA to extract independent components (ICs) representing shared brain networks across subjects. Group-level independent components are shown in Fig. S1. Dual regression was then applied in two stages: first, group-level IC maps were used as spatial regressors to estimate subject-specific time courses, and second, these time courses were used to back-reconstruct subject-specific spatial maps for each IC. Gaussian smoothing with a 3 mm sigma was applied to reduce noise and enhance sensitivity to group differences. Statistical analysis involved voxel-wise comparisons using Randomise, a non-parametric permutation testing method, with multiple comparisons corrected using threshold-free cluster enhancements (TFCE).

Individual spatial maps were obtained for each participant using dual regression from preprocessed functional data. For group-level

Table 1
Tests included in each cognitive domain.

Cognitive domains	Variables
<i>Learning and memory</i>	Free and Cued Selective Reminding Test immediate recall and delayed recall Rey Osterrieth Complex Figure immediate recall and delayed recall
<i>Language</i>	Boston Naming Test, semantic fluency
<i>Attention and processing speed</i>	Digit Span Forward, Digit Span Backwards, Trail Making Test part A
<i>Executive Functions</i>	Letters and Numbers, Trail Making Test part B, phonetic fluency (P,M,R)

comparisons, we extracted the total Z-score within each Yeo 7-network mask to summarize component activity within canonical functional networks. This allowed consistent inter-subject comparison in a common functional reference space.

For the diffusion data, major tract integrity metrics was compared in two different groups: Group 1, consisting of 17 subjects with at least one low score, and Group 0, comprising 18 subjects with no low scores. Comparisons were performed between the groups using Tract-Based Spatial Statistics (TBSS) on Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps. The preprocessing steps included motion correction, eddy current correction, and brain extraction, followed by the generation of FA and MD maps for each subject. Skeletonization was performed by aligning all FA images to a common template using non-linear registration, creating a mean FA image, and deriving a white matter skeleton representing core tracts shared across subjects. Each subject's FA and MD data were projected onto this skeleton to reduce misalignment errors. TBSS inherently avoids smoothing to preserve tract boundaries. Statistical analysis involved voxel-wise comparisons between groups using Randomise, a non-parametric permutation testing approach, with corrections for multiple comparisons applied via threshold-free cluster enhancements (TFCE). Data are available upon reasonable request from the corresponding author.

3. Results

The sample included 40 participants (75 % women). Participants' age ranged from 58 to 82 and years of education from 4 to 22 (not including University for Seniors). For the entire sample there were no differences in MMSE, IADL, education and GDS. Only differences in age by sex were statistically significant (men = 72.5 (SD = 5.72); women = 67.73 (SD = 5.88); $t(38) = 2.23, p = 0.031$).

3.1. Neuropsychological assessment

There were no statistically significant sex differences in tests performance, medical history (all p 's > 0.05) or medication (all p 's > 0.05). Twenty-one participants (52.5 %) had at least one low score across cognitive domains. Differences in demographics are shown in Table 2 and differences in composites scores are shown in Table 3.

3.2. Neuroimaging data

Total brain volume, right and left hemisphere and regional volumes (Fig. 1), white matter integrity using FA and MD values and functional connectivity (Fig. 2) were cross-sectionally analyzed between groups, and no statistically significant differences were found. The binomial logistic regression showed that there was no association between total brain volume (OR = 0.964, 95 % CI 0.84–1.10, $p = 0.583$) or left and right hemisphere volume (OR = 1.00, 95 % CI 0.999–1.00, $p = 0.615$, OR = 0.894, 95 % CI 0.60–1.33, $p = 0.579$) and the odds of presenting at least one low score across cognitive domains. After controlling for demographics in the models (age, sex, and years of education), only age (OR = 0.17, $p = 0.021$) was associated with the odds of obtaining at least one composite low score.

Table 2
Descriptive statistics for demographic and clinical measures by group.

	Group 0	Group 1+	t-statistic	p-value
Age	6.68 (6.36)	70.95 (5.28)	−2.31	0.026
Education	13.53 (2.81)	13.43 (4.74)	0.078	0.938
MMSE	28.95 (0.91)	28.52 (1.50)	1.063	0.295
GDS	3.58 (3.97)	5.48 (3.52)	−1.60	0.118

Group 1+: one or more composite score $z \leq -1.5$; MMSE: Mini-Mental State Examination. GDS: Gesavage Depression Scale.

Table 3
Means and standard deviations of composite scores by group.

	Group 0	Group 1+	t-statistic	p-value
Learning and memory	−0.33 (0.77)	−1.09 (1.12)	2.47	0.018
Language	0.11 (0.95)	−0.80 (1.35)	2.44	0.020
Attention and PS	1.11 (1.40)	−0.63 (1.55)	3.73	< 0.001
EF	1.02 (0.89)	−1.06 (1.94)	4.28	< 0.001

Group 1+: one or more composite score $z \leq -1.5$

4. Discussion

The aim of the present work was to explore the relationship between brain volumetry, structural and functional connectivity and cognitive performance in a group of Spanish cognitively active older adults. Previous studies on healthy aging have reported a consistent reduction in brain cortical and subcortical volume, which correlates with deterioration in certain cognitive abilities. For example, reduced hippocampal and entorhinal cortex volume has been reported in older adults in association with worse performance in verbal memory tests, whilst reduced left superior temporal and frontal cortex was associated with worse semantic memory and executive function performance respectively [37]. In our work with healthy and cognitively active adults, the results show no association between brain volume and the risk of presenting low scores in at least one cognitive domain and an absence of association between brain volume and cognitive performance, which reflects the benefits of engaging in cognitively stimulating activities during aging.

Previous studies on healthy aging have reported an association between low FA and high MD with worse cognitive performance [38,39,40]. Unlike previous works comparing good vs. poor performers [41], we found no association between diffusion white-matter integrity and cognitive performance, nor were there significant differences in the activation of major resting state networks between individuals with no composite low scores and individuals with at least one composite low score. Since evidence shows that that expected pattern during aging is a decrease of cognitive performance together with changes in different brain parameters [42,43], the absence of an association between neuroimaging data and cognitive performance suggests that highly active older adults do not follow the brain and cognitive trajectory of changes expected in same-age adults in the general population, which might indicate a potential protective mechanism linked to brain activity in this cognitively active population.

Two mechanisms that positively impact brain changes and modulate the effects of brain deterioration have been widely described in the aging literature: Brain reserve and cognitive reserve. Brain stimulation throughout the lifespan, through learning, participation in social activities, or engaging in physical exercise, generates a broader brain reserve. In the same way, cognitive reserve is developed with lifetime experiences, education, occupational complexity, and cognitively, socially, and physically stimulating activities [44,45,46]. The absence of statistically significant differences suggests that obtaining low scores might be detected before observable brain changes have occurred, thereby motivating future longitudinal studies to track these patients over time. Additionally, it emphasizes an important distinction: while neuroimaging alterations often precede cognitive changes in neurodegenerative conditions, this pattern does not appear to hold in the population of super-agers. In this group, cognitive impairments seem to emerge before detectable imaging alterations, whether morphological, structural (tract-related), or functional. However, as showing low scores could only reflect normal cognitive variability [47,35], further longitudinal studies are warranted to unravel changes in cognitive functioning and brain structure and function.

Our results are in line with previous works on older adults referred to as superagers, those with performance on cognitive tests as good as that of healthy adults 20–30 years younger [48,49]. Superagers show a better

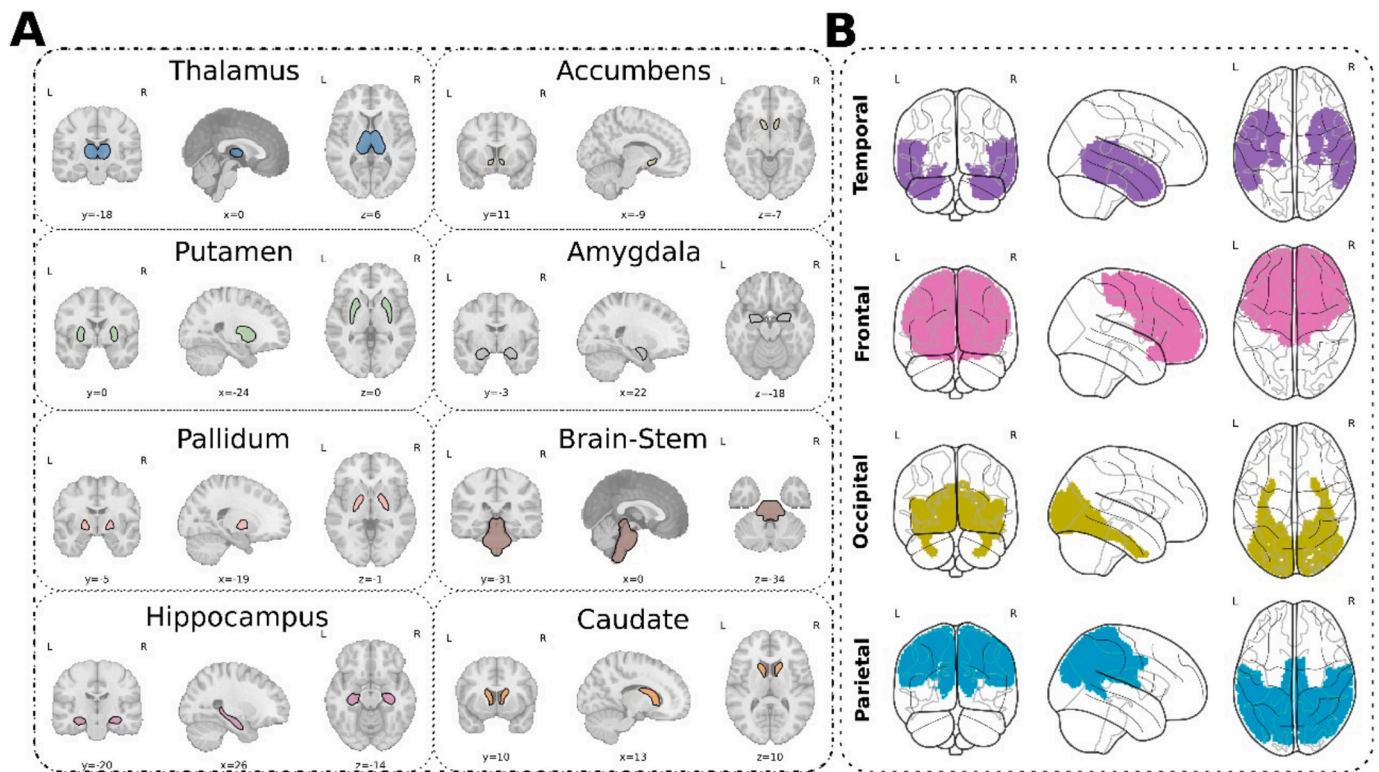


Fig. 1. Morphometry Based Analysis Atlases. A. Brain subcortical regions obtained from the Harvard-Oxford Subcortical Atlas. Volumetric Analysis was performed to these areas using the FIRST tool from FSL. B. Visualization of the four main lobes of the brain—Temporal, Frontal, Occipital, and Parietal—based on the grouping of 36 regions from the Desikan-Killiany atlas. The **Temporal Lobe** comprised by the Superior Temporal Sulcus, Entorhinal Cortex, Inferior Temporal Cortex, Middle Temporal Cortex, Parahippocampal Gyrus, Superior Temporal Gyrus, Temporal Pole, and Transverse Temporal Gyrus (Heschl's Gyrus). The **Frontal Lobe** includes the Caudal Anterior Cingulate Cortex, Caudal Middle Frontal Cortex, Lateral Orbitofrontal Cortex, Medial Orbitofrontal Cortex, Paracentral Lobule, Pars Opercularis, Pars Orbitalis, Pars Triangularis, Precentral Gyrus, Rostral Anterior Cingulate Cortex, Rostral Middle Frontal Cortex, Superior Frontal Gyrus, and Frontal Pole. In the **Occipital Lobe**, we find the Cuneus, Fusiform Gyrus, Lateral Occipital Cortex, Lingual Gyrus, and Pericalcarine Cortex (Primary Visual Cortex). Lastly, the **Parietal Lobe** consists of the Inferior Parietal Lobule, Isthmus of the Cingulate Gyrus, Postcentral Gyrus, Posterior Cingulate Cortex, Precuneus, Superior Parietal Lobule, and Supramarginal Gyrus. Cortical thickness of each of these regions was calculated using FREESURFER *recon_all* procedure.

preservation of brain structure and WM integrity [50], as well as better connectivity in different brain networks [46] than do typical older adults. Cortical atrophy has been correlated with impairment in language in the left temporal pole, fusiform gyrus, and amygdala [39]. WM integrity alteration with aging has also been associated with worsening cognitive performance, primarily impairing memory and executive functions. Lower performance in episodic memory have been associated with lower FA in the ILF, cingulum [39,40], the UF, SLF, thalamic radiations, and dorsal cingulum bundle [51,40]. Lower performance in tests of attention and executive function have been related to lower FA in anterior and posterior cingulum, ILF [52,39], SLF and UF. Information processing speed has been correlated with FA in the cingulum, fornix, ILF and SLF [40]. Lower performance on language tests have been associated with lower FA in the ILF and posterior cingulum [52,39], and lower performance on visual-spatial processing with lower FA in the posterior cingulum tract, the fornix [39] and in the ILF [52]. Lower performance on episodic memory, attention, executive functions, information processing speed, language and visuospatial processing have been associated with lower FA in different association fibers, such as ILF, SLF, limbic system fibers (e.g., cingulum and thalamic radiations) [52,39,51,40]. Since we did not find a worse brain structure or connectivity in participants showing one or more low composite scores, it is then feasible to consider that participation in highly cognitively stimulating activities might act as a protective factor against cognitive impairment by preserving brain volume, connectivity and functioning. Supporting our results, a beneficial effect on white matter microstructure and cognition in older adults engaged in leisure and social activities have been described in previous research [53] as well as after persistent

cognitive activity through cognitive training programs [54].

Despite brain changes expected with aging, the absence of an association between cognitive performance and neuroimaging data in this active population supports the hypothesis that a greater cognitive reserve may imply the development of a greater brain reserve, with better brain resistance to impairment. The results of the present work suggest that participation in stimulating cognitive activities at older ages, such as University for Seniors, could be acting as a protective factor and engagement in these programs might be a potential strategy for keeping cognitively active during aging and to promote healthy brain aging and prevent age-related cognitive impairment [17,16].

4.1. Limitations

The results of this study should be interpreted in light of the following limitations. Our clinically oriented MRI acquisition protocols present limitations, including the use of a single phase-encoding direction in fMRI, which may introduce region-specific distortions affecting functional connectivity analyses, and the use of standard in-hospital multishell diffusion protocols, which limits the ability to resolve complex fiber crossings. For group-level comparisons, Yeo resting-state network masks were used to aggregate subject-specific Z-maps obtained via dual regression from individual functional data; while this facilitates inter-subject comparison, it may introduce constraints by imposing predefined spatial boundaries over data-driven components. Some neuropsychological domains (e.g., visuospatial and visuoconstructional functioning, processing speed or perceptual abilities) that are impaired in dementias other than AD [55] could not be included as

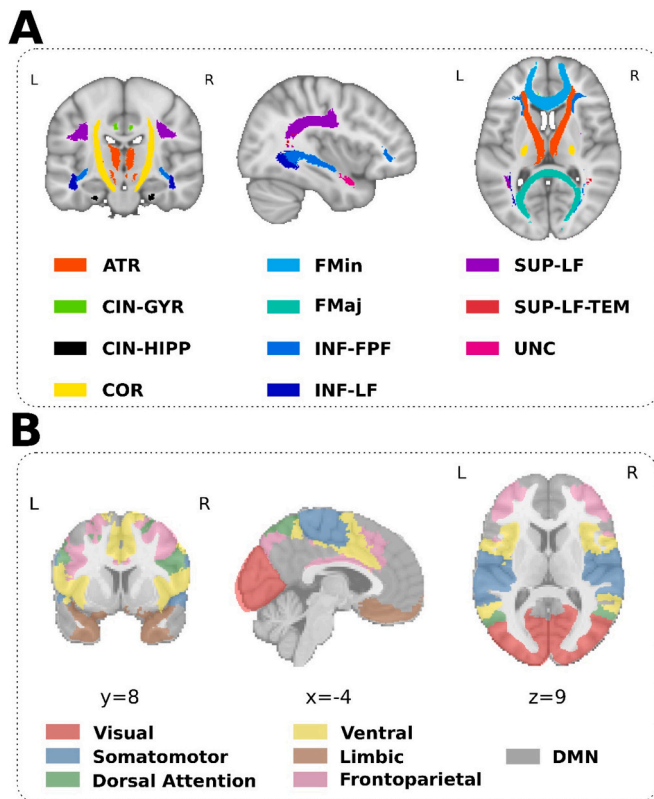


Fig. 2. A. White Matter Brain Tracts from the JHU ICBM Maxprob THR25 2 mm Tracts Atlas. ATR: Anterior Thalamic Radiation. CIN-GYR: Cingulum (cingulate gyrus). CIN-HIPP: Cingulum (Hippocampus). COR: Corticospinal Tract. Fmin: Forceps Minor. FMaj: Forceps Major. INF-FPF: Inferior Frontal-Occipital Fasciculus. INF-LF: Inferior Longitudinal Fasciculus. SUP-LF: Superior Longitudinal Fasciculus. SUP-LF-TEM: Superior Longitudinal Fasciculus (Temporal Part). UNC: Uncinate Fasciculus. Mean Fractional Anisotropy was calculated for each tract using FSL. B. Seven Yeo's Resting State Networks Functional Atlas. For each of the RSNs mask we calculate mean values of activation.

composite domains. MRI and neuropsychological analyses have not been contrasted with less active samples from the general population, which precludes analyzing whether being cognitively active preserves brain structure or preserved brain structures allows individuals to engage in cognitive activities. Finally, as a cross-sectional study, we were not able to analyze whether engaging in highly cognitively stimulating activities protects against longitudinal decline. Further longitudinal research to further explore differences in volumetry and brain connectivity between samples of cognitively active older people and older people from the general population are needed, as well as comparisons between cognitively active older adults and clinical samples.

4.2. Clinical implications

Our results have clinical implications to promote healthy aging. This research shows that cognitive performance variability in a battery with several tests is normal among cognitively healthy adults. Since this normal variability shows no association with brain features such as FA or MD, the results of the present work suggest that active lifestyles foster healthy brain aging, with optimal brain function. Participation in cognitive stimulating activities might then be a possible factor for brain maintenance and determinant for increasing the cognitive reserve and cognitive impairment resistance during aging. Since people who attend UPS tend to participate not only in the academic programs but in variety of activities such as physical activity, seminars, volunteering, workshops and trips [56,57] that keep them very physical and cognitively active in their daily life, health and social policies should promote participation

in these activities as preventing factor against cognitive decline during aging. This research provides further insights into active aging features and highlights the need for more long-term research in cognitively active population.

CRedit authorship contribution statement

Clara Iñesta: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Beatriz Bonete-López:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Javier Oltra-Cucarella:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Borja Camino-Pontes:** Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Jesús M. Cortés:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Juan Carlos Arango-Lasprilla:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Esther Sitges-Maciá:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2025.123658>.

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