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Structural neuroimaging changes associated with subjective cognitive decline from a clinical sample

Mario Riverol [a,c,*], Mirla M. Ríos-Rivera [a,d], Laura Imaz-Aguayo [a], Sergio M. Solis-Barquero [b], Carlota Arrondo [a], Genoveva Montoya-Murillo [a], Rafael Villino-Rodríguez [a], Reyes García-Eulate [b], Pablo Domínguez [b,c], Maria A. Fernández-Seara [b,c]

[a] Department of Neurology, Clínica Universidad de Navarra, Pamplona 31008, Navarra, Spain
[b] Department of Radiology, Clínica Universidad de Navarra, Pamplona 31008, Navarra, Spain
[c] Instituto de Investigación Sanitaria de Navarra, Pamplona 31008, Navarra, Spain
[d] School of Medicine, Universidad Autónoma de Chiriquí, David 4001, Chiriquí, Panama

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ABSTRACT

Background: Alzheimer's disease (AD) is characterized by progressive deterioration of cognitive functions. Some individuals with subjective cognitive decline (SCD) are in the early phase of the disease and subsequently progress through the AD continuum. Although neuroimaging biomarkers could be used for the accurate and early diagnosis of preclinical AD, the findings in SCD samples have been heterogeneous. This study established the morphological differences in brain magnetic resonance imaging (MRI) findings between individuals with SCD and those without cognitive impairment based on a clinical sample of patients defined according to SCD-Initiative recommendations. Moreover, we investigated baseline structural changes in the brains of participants who remained stable or progressed to mild cognitive impairment or dementia.

Methods: This study included 309 participants with SCD and 43 healthy controls (HCs) with high-quality brain MRI at baseline. Among the 99 subjects in the SCD group who were followed clinically, 32 progressed (SCDp) and 67 remained stable (SCDnp). A voxel-wise statistical comparison of gray and white matter (WM) volume was performed between the HC and SCD groups and between the HC, SCDp, and SCDnp groups. XTRACT ATLAS was used to define the anatomical location of WM tract damage. Region-of-interest (ROI) analyses were performed to determine brain volumetric differences. White matter lesion (WML) burden was established in each group.

Results: Voxel-based morphometry (VBM) analysis revealed that the SCD group exhibited gray matter atrophy in the middle frontal gyri, superior orbital gyri, superior frontal gyri, right rectal gyrus, whole occipital lobule, and both thalami and precunei. Meanwhile, ROI analysis revealed decreased volume in the left rectal gyrus, bilateral medial orbital gyri, middle frontal gyri, superior frontal gyri, calcarine fissure, and left thalamus. The SCDp group exhibited greater hippocampal atrophy ($p < 0.001$) than the SCDnp and HC groups on ROI analyses. On VBM analysis, however, the SCDp group exhibited increased hippocampal atrophy only when compared to the SCDnp group ($p < 0.001$). The SCD group demonstrated lower WM volume in the uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus, anterior thalamic radiation, and callosum forceps than the HC group. However, no significant differences in WML number ($p = 0.345$) or volume ($p = 0.156$) were observed between the SCD and HC groups.

Abbreviations: AD, Alzheimer's disease; ANCOVA, Analysis of Covariance; ANOVA, analysis of variance; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DARTEL, Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra; FLAIR, Fluid-Attenuated Inversion Recovery; FWE, family-wise error; GDS, Geriatric Depression Scale; GM, Gray Matter; HC, Healthy Control; IDDD, Interview for Deterioration in Daily Living Activities in Dementia; IQR, Interquartile range; LST, Lesion Segmentation Toolbox; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; MPRAGE, Magnetization-prepared Rapid Gradient-echo; MRI, Magnetic Resonance Imaging; MTL, Medial Temporal Lobe; ROI, Regions of Interest; SCD, Subjective Cognitive Decline; SCD-I, Subjective Cognitive Decline-Initiative working group; SCDnp, Subjective Cognitive Decline Non-progressors; SCDp, Subjective Cognitive Decline Progressors; SD, Standard deviations; SPM, Statistical Parametric Mapping; TE, Echo Time; TI, Inversion Time; TR, Repetition Time; VBM, Voxel-Based Morphometry; WM, White Matter; WMLs, White Matter Lesions.

* Corresponding autor at: Department of Neurology, Clínica Universidad de Navarra, Av. de Pío XII, 36, 31008 Pamplona, Navarra, Spain.
E-mail address: mriverol@unav.es (M. Riverol).

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Conclusions: The SCD group showed brain atrophy mainly in the frontal and occipital lobes. However, only the SCDp group demonstrated atrophy in the medial temporal lobe at baseline. Structural damage in the brain regions was anatomically connected, which may contribute to early memory decline.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive deterioration of cognitive function, leading to the loss of functional independence. It is also the most frequent cause of dementia in older adults (Scheltens et al., 2016). Studies have found that some individuals with subjective memory complaints exhibit clinical progression to mild cognitive impairment (MCI) or dementia due to AD (Jessen et al., 2014; Molinuevo et al., 2017; Rabin et al., 2017). According to the National Institute on Aging–Alzheimer's Association criteria, subjective cognitive decline (SCD) can be considered as stage 2 within the AD continuum (Jack et al., 2018). Considering the lack of standardized criteria for defining SCD, in 2014, the SCD-Initiative working group (SCD-I) proposed a conceptual framework and a set of terminologies and features for SCD relying on two main criteria: (1) self-experienced persistent decline in previously normal cognitive capacity unrelated to an acute event and (2) normal performance on standardized cognitive tests, which are used to classify MCI, adjusted for age, sex, and education. Additionally, this decline cannot be explained by a psychiatric or neurological disease (apart from AD), medical disorder, medication, or substance use (Jessen et al., 2014; Molinuevo et al., 2017). Although the SCD-I criteria have been recommended for research contexts, other methods are currently being used (Morrison et al., 2022;33:102923.).

The identification of potential biomarkers suitable for the diagnosis of early-stage AD has involved the study of clinical features, non-modifiable and modifiable factors, cognitive testing, cerebrospinal fluid analysis, and various neuroimaging modalities (Rabin et al., 2017; Sperling et al., 2011; Dubois et al., 2014). Magnetic resonance imaging (MRI) has been extensively employed to investigate structural brain changes associated with neurodegenerative disorders because of its high soft tissue resolution (Chen et al., 2023). To assess the gray matter (GM), T1-weighted imaging has been used primarily with volumetric analysis of delineated regions-of-interest (ROI), voxel-based morphometry (VBM) comparisons, and cortical thickness comparisons based on the cortical surface area, each of which have their own advantages and limitations (Voormolen et al., 2010; Wang et al., 2020; Arrondo et al., 2022). In contrast, white matter lesions (WMLs) are better evaluated using T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (Barkhof and Scheltens, 2002).

Evidence regarding structural changes observed in the brains of individuals with SCD remains inconsistent (Rivas-Fernández et al., 2023). Indeed, some studies have reported that decreased hippocampal volume was not only a consistent finding in participants with SCD (Wang et al., 2020; Hafkemeijer et al., 2013) but also a marker of clinical progression (Ebenau et al., 2022), whereas others found no significant differences in hippocampal volume between those with SCD and healthy controls (HCs) (Dong et al., 2020; Platero et al., 2019). In fact, a recent systematic review analyzing 51 studies evaluating GM volumetric changes on brain MRI in patients with SCD (Arrondo et al., 2022) found that regardless of the analysis technique used, the medial temporal lobe (MTL) was the region where the greatest atrophy occurred in SCD subjects; however, at least half of the studies did not find significant differences. This finding is consistent with the heterogeneous results reported previously. One possible explanation for the diverse results among studies could be the differences in the approaches used to define SCD. Wang et al. (Wang et al., 2020) found differences in SCD operationalization across studies. In particular, only 8 % of studies examined structural changes in people with SCD using the SCD-I recommendations, even those conducted after 2014, when a conceptual framework for SCD research was proposed. Variability in brain atrophy and longitudinal cognitive trajectory is affected by the method used to define SCD (Morrison et al., 2022;33:102923.; Vogel et al., 2016). Differences in sample populations and inclusion criteria or the low pathological manifestations of SCD in the ultra-early phase of AD could also explain the discrepant results among studies. In this context, subjects with SCD from a memory clinic setting have a higher risk of developing cognitive impairment than the general population (Rodríguez-Gómez et al., 2015). Moreover, Jessen et al. (Jessen et al., 2023) found an amyloid positivity rate of 39 % in patients with SCD from memory centers and 27.2 % in the control group, suggesting that SCD associated with amyloid-positive pathology and memory center consultation was highly indicative of being in stage 2 of the AD continuum.

Research on white matter (WM) in subjects with SCD has revealed widespread disruptions in the hippocampus, entorhinal cortex, parahippocampal gyrus, uncinate fasciculi, longitudinal fasciculi, and corpus callosum (Wang et al., 2020; Li et al., 2016). Previous multimodal neuroimaging analysis that simultaneously assessed GM and WM abnormalities in the SCD group had revealed structural abnormalities in bilateral middle temporal gyri, frontal and occipital lobes, and the superior parietal lobule for the GM and the anterior thalamic radiation and superior longitudinal fasciculus for the WM (Liang et al., 2021), which suggests an interrelationship between the GM and WM in the degenerative process that could potentially lead to early memory decline (Chen et al., 2023; Selnes et al., 2012;8(5);Suppl:S112–S121.). Other SCD studies have found abnormal patterns in the GM and WM similar to that in MCI or intermediate damage patterns between HC and those with MCI (Wang et al., 2020; Wang et al., 2012). Overall, further investigations are needed to better understand the order of alterations and the relationship between GM and WM alterations during the SCD stage (Wang et al., 2020).

In addition, WMLs are prevalent on MRI scans of the aging brain and could reflect cerebral small vessel disease (Wardlaw et al., 2013). Several studies have found associations between WMLs and a reduction in brain volume and cognitive impairment (Lam et al., 2017; Gunning-Dixon and Raz, 2000; Prins and Scheltens, 2015). Previous studies have reported a specific relationship between larger WML volumes and lower executive functions in SCD, MCI, and HC (Qi et al., 2019; Caillaud et al., 2020). Thus, the relationship between WMLs and executive functions does not seem to be exclusive to MCI and SCD and may be relevant to a broader range of individuals (Qi et al., 2019; Caillaud et al., 2020). However, the relationship between WML volume and the number of memory complaints in patients with SCD also appear to increase the risk of clinical progression (van Rooden et al., 2018; Benedictus et al., 2015). Nonetheless, evidence shows that the spatial distribution of the WMLs has a differential impact on cognitive function (Lam et al., 2017). Thus, WML severity in the periventricular regions, subcortical regions, or cholinergic pathways has been correlated with cognitive decline in aging people (Prins and Scheltens, 2015; Qi et al., 2019).

The present study aimed to establish the morphological differences associated with SCD on brain MRI at diagnosis and their association with clinical progression in a clinical sample of patients defined according to SCD-I recommendations. Precisely, we examined baseline volumetric differences in GM and WM between patients with SCD and HCs. We also compared baseline GM and WM volumes between HCs and those with SCD who exhibited clinical progression (SCDp) or remained cognitively stable (SCDnp) at follow-up. GM volume was assessed using two common techniques for brain volumetric analyses, namely VBM and ROI. We further determined the WML burden in each group.

2. Materials and methods

2.1. Participants and measurements

We retrospectively selected 309 subjects with a clinical diagnosis of SCD according to the SCD-I criteria and high-quality brain MRI. All participants were recruited from the Memory Clinic at the University of Navarra Clinic between 2001 and 2017 and evaluated by a neurologist experienced in cognitive disorders. All participants provided written informed consent prior to study participation.

Specifically, we examined the changes in GM, WM, and WML associated with SCD at baseline, and in the participants who had stable disease or showed clinical progression at follow-up. HCs (n = 43; age, 68.5 ± 6.0 years) comprised volunteers recruited through an advertisement who had no cognitive decline and normal performance on standardized cognitive test adjusted for age, sex, and education.

All patients with SCD (n = 309; age, 65.4 ± 9.4 years) satisfied the research criteria proposed by SCD-I. They complained of memory decline despite having a normal performance on standardized neuropsychological tests. Among the 309 participants, 99 who completed one or more follow-up visits up to January 2020 after baseline were analyzed through a retrospective longitudinal follow-up at our unit. During the follow-up visits, the patients were evaluated by a neurologist, and a neuropsychological assessment was performed to assess clinical progression, which included the same neuropsychological evaluation criteria as the initial evaluation. Notably, 32 participants progressed to amnestic MCI (n = 24) or dementia (n = 8), based on the 2011 NIA-AA clinical criteria (Albert et al., 2011; McKhann et al., 2011), and were classified as SCD progressors (SCDp; n = 32; age, 71.0 ± 5.8 years). Interestingly, none of the patients with SCD who exhibited progression had another type of dementia other than AD based solely on clinical diagnostic criteria without assessing for AD biomarkers of amyloid or tau deposition.

All participants underwent the following initial assessment: (1) medical and history review, (2) interview with a family member or friend, (3) general examination, and (4) neurological examination and a neuropsychological assessment. The medical history and variables included age at SCD diagnosis, sex, education level, and history of medical conditions such as hypertension, diabetes mellitus, hypercholesterolemia, smoking habit, and cardiovascular or cerebrovascular disease. General medical examination included a laboratory test (full blood count, biochemistry, vitamin B12, serum folate, glucose, lipids, syphilis serology, and thyroid function) and brain MRI (1.5-T MRI; T1- and T2-weighted 2D FLAIR). The standardized cognitive tests to evaluate cognitive status at baseline and follow-up included a comprehensive test battery that evaluated the following domains: global cognitive function (Mini-Mental State Examination [MMSE]) (Folstein et al., 1975); episodic verbal memory (word list learning, recall, and recognition), and episodic visual memory (figure recall) (The Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Task [CERAD] neuropsychological battery) (Morris et al., 1988); attention and executive function (Trail Making Test parts A and B) (Reitan and Wolfson, 1993); phonetic fluency (words with letter p) (Ramier and Hecaen, 1970); cognitive flexibility and cognitive interference (The Stroop Color and Word Test) (Golden, 1978); semantic fluency (animal categories) (Ramier and Hecaen, 1970); and the 60-item Boston naming test (Kaplan et al., 2001). Depression and activities of daily living function were evaluated using the 30-question Geriatric Depression Scale (GDS) (Yesavage et al., 1982) and Interview for Deterioration in Daily Living Activities in Dementia (IDDD) (Teunisse et al., 1991), respectively. Normal cognition was operationalized by a performance exceeding − 1.5 standard deviations (SD) from the normal range adjusted for age, sex, and education on all tests (Molinuevo et al., 2017).

The exclusion criteria for patients were as follows: (1) age less than 56 years, (2) MCI or dementia, (3) major neurological disorders or systemic illnesses that could cause cognitive impairment, (4) current or past major psychiatric disease, such as schizophrenia, major depression, or bipolar disorder), (5) history of alcohol or substance abuse, (6) significant brain MRI abnormalities, such as brain tumors, large cerebral infarct, or bleeding, and (7) history of head trauma with loss of consciousness. Unimpaired cognitive performance in the HC group was defined using the same definition as the SCD group. All records were reviewed in a multidisciplinary consensus meeting to establish a clinical diagnosis.

2.2. MRI acquisition and processing

Images were acquired using two 1.5-T MRI scanners. Participants underwent MRI using either a 1.5-T Magnetom Symphony or 1.5-T Magnetom Aera instrument (Siemens, Erlangen, Germany) for baseline but not follow-up evaluation. The following two different sequences were acquired:

- A T1-weighted three-dimensional (3D) magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters for the analysis of GM and WM volumes: inversion time (TI), 1,100 ms; repetition time (TR), 1900 ms; and echo time (TE), 4.0 ms. T1-weighted images had two different resolutions: 1.0 × 1.0 × 1.5 $mm^3$and 0.5 × 0.5 × 1.0 mm^3.
- T2-weighted 2D FLAIR sequences with the following parameters to quantify WMLs: Tis, 2500/2200 ms; TEs, 125/121/119 ms; TRs, 8150/8500/9000 ms; and resolution, 1.0 × 1.0 × 5.0 mm^3/0.9 × 0.9 × 5.0 mm^3/0.5 × 0.5 × 5.0 mm^3.

The sequences were acquired using different parameters given the varying clinical protocols employed throughout the 16-year study period.

Image preprocessing was performed using Statistical Parametric Mapping (SPM version 12, Welcome Trust Center for Neuroimaging, University College London, United Kingdom) executed in MATLAB (MathWorks, MA, United States). Images were converted from the standard Digital Imaging and Communication in Medicine format to the Neuroimaging Informatics Technology Initiative format. 3D MPRAGE images were manually reoriented along the anterior commissure line, followed by a segmentation procedure aimed at extracting GM and WM probability maps from the images. The maps were normalized using the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) algorithm described by Ashburner and Friston (Ashburner and Friston, 2005; Ashburner, 2007). DARTEL was used to create GM and WM templates from the maps. GM and WM probability maps were normalized with respect to the template and modulated to preserve the total amount of signal from each region. The normalized and modulated probability maps were smoothed using an 8 × 8 × 8 mm^3 full-width half-maximum Gaussian kernel. Therefore, 3D-normalized probability maps of GM and WM were obtained for each participant.

FLAIR images were processed using the lesion segmentation toolbox (LST) for SPM12 (https://www.applied-statistics.de/lst.html). WMLs were identified using the Lesion Prediction Algorithm implemented in the LST. From the segmented lesions, different metrics of interest were obtained, such as the number of lesions and total lesion volume (in mL).

2.3. Statistical analysis

All analyses were performed using Stata 12.1 (StataCorp. 2011; Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP).

Demographic, medical, and neuropsychological data are expressed as mean ± standard deviation, unless otherwise indicated. Comparisons of quantitative characteristics between patients with SCD and those with HCs were performed using an independent-samples *t*-test. For comparisons of two or more means, analysis of variance (ANOVA) was performed. Tukey's test was used to compare the differences between each

pair of means. Comparisons of qualitative characteristics between the groups were performed using the chi-square test or Fisher's exact test (as required by the expected number of events). In all cases, a P value of $<$ 0.05 indicated statistical significance.

Considering that WML data distributions were right-skewed, the values were log transformed before statistical analysis. Differences in WML volume and lesion number between patients with SCD and controls were analyzed using a general linear model with group (patients with SCD and HCs) as the independent variable and several confounding variables (i.e., age, sex, education level, and type of scanner). Subsequently, an analysis of covariance (ANCOVA) was performed to evaluate differences across groups (HC, SCDnp, and SCDp groups) using the same variables listed above as covariates.

2.4. VBM analysis

First, a voxel-wise statistical comparison of GM volume was performed between the HC group and all participants with SCD using a two-sample t-test (unequal variances), with age, sex, education level, type of scanner, and total intracranial volume being applied as covariates. The same method was used to analyze the WM volume.

Subsequently, one-way ANOVA was conducted to compare GM and WM volumes between the three groups (i.e., HC, SCDnp, and SCDp groups). Age, sex, education level, scanner type, and intracranial volume were also used as covariates. ANOVA was followed by post hoc contrast across groups. Finally, the clusters obtained were compared using XTRACT ATLAS (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/XTRACT#XTRACTAtlases) to define the anatomical location of the WM tract differences.

For multiple comparisons, cluster-extent-based thresholding was performed. First, a P value of $<$ 0.001 was employed to generate the clusters, after which a P value of $<$ 0.05, after family-wise error (FEW), was used to select the significant clusters (Woo et al., 2014). Given that no voxels survived the FWE cluster correction during the comparison of the SCDnp and SCDp groups, an uncorrected threshold of $P < 0.001$ (cluster size $>$ 50) was applied.

Finally, to assess the relationship between GM volume and neuropsychological test performance in the SCD patient group, multiple regression analysis was implemented using SPM while controlling for the same covariates used in the previous analysis. Correlations were evaluated using the following neuropsychological tests: MMSE, GDS, CERAD, phonetic fluency (words with p), and semantic fluency (animal categories). Results of this analysis are presented in the Supplementary Material (See Supplementary Fig. 1 and Supplementary Tables 1–3).

2.5. Region-of-interest analysis

As a complement to the voxel-wise analysis, we examined the volumetric differences in GM at the ROI level. The analyses were performed using R for Statistical Computing (https://www.r-project.org). ROIs were defined using automated anatomical labeling atlas 2 (AAL2) (https://www.gin.cnrs.fr/en/tools/aal/). Average GM volumes were extracted within the 120 ROIs. For each ROI, first GM volumes were compared between patients with SCD and HCs using a general linear model, with group (SCD and HC) as the independent variable and age, sex, education level, scanner type, and total intracranial volume as covariates to control possible confounding effects. Differences were considered significant at $P < 0.0004$ (obtained after Bonferroni correction for multiple comparisons, considering the number of ROIs). Subsequently, ANCOVA was performed to evaluate the differences across groups (HCs, SCDnp, and SCDp) using the variables listed above as covariates. When the ANCOVA P value was $<$ 0.0004 (applying Bonferroni correction), post hoc contrasts were assessed across the groups.

2.6. Data availability

All data supporting the findings of this study are available within the article and its supplementary material.

3. Results

3.1. Comparison of general clinical data

We analyzed the baseline structural neuroimaging databases of 309 patients with SCD and compared them with those of 43 healthy older adults. Among the 309 patients, 99 underwent longitudinal assessment (SCDp = 58.6 ± 41.1 and SCDnp = 48.2 ± 37.8 months) and completed one or more evaluations by a neurologist after baseline. A total of 32 participants showed clinical progression to MCI (n = 24) or dementia due to AD (n = 8), whereas 67 remained stable.

Among the entire cohort, participants of the SCD group were younger in age (65.4 ± 9.4 vs. 68.5 ± 6.0 years; $t = 2.11$, $P < 0.001$) and had a higher education level (11.8 ± 3.3 vs. 9.8 ± 2.6 years of education; $t = -3.77$, $P < 0.001$) than the HC group. Moreover, we examined the association of vascular risk factors with cognitive impairment and WMLs. Interestingly, the SCD group had more cases of diabetes (13 % vs. 0 %; $\chi^2 = 6.46$, $P = 0.011$), hypercholesterolemia (57 % vs. 35 %; $\chi^2 = 7.41$, $P = 0.006$), past or present smoking habit (34 % vs. 14 %; $\chi^2 = 7.01$, $P = 0.008$), and cardiovascular disease (8.7 % vs. 0 %; $\chi^2 = 4.07$, $P = 0.044$) than the HC group. No significant differences in sex (50 % vs. 42 % women; $\chi^2 = 1.04$, $P = 0.31$), hypertension (48 % vs. 46.5 %; $\chi^2 = 0.04$, $P = 0.83$), or cerebrovascular disease (3.6 % vs 2.3 %; $\chi^2 = 0.17$, $P = 1.0$) were observed between the two groups. Regarding the neuropsychological evaluation, the SCD group had a worse performance on the MMSE (28.3 ± 1.8 vs. 29.0 ± 1.1; $t = -3.48$, $P < 0.001$), verbal memory (delay recall: 5.1 ± 1.8 vs. 5.8 ± 1.7; $t = -3.75$, $P < 0.001$), and semantic (16.9 ± 5.2 vs. 19.1 ± 5.4; $t = -3.53$, $P < 0.001$) and phonemic (13.5 ± 5.0 vs. 14.2 ± 5.1; $t = -2.19$, $P = 0.029$) fluencies and had more cases with depressive symptoms (GDS: 9.7 ± 6.4 vs. 4.2 ± 3.4; $t = 5.32$, $P < 0.001$) than did the HC group (Table 1).

Comparison between the SCDp, SCDnp, and HC groups revealed significant differences in age (71.0 ± 5.8 vs. 64.9 ± 8.3 vs. 68.5 ± 6.0, years, respectively; F = 8.76, $P < 0.001$), education (12.7 ± 3.4 vs. 11.4 ± 3.3 vs. 9.8 ± 2.6, years of education, respectively; F = 8.3, $P < 0.001$), hypercholesterolemia (24 % vs. 38 % vs. 15 %, respectively; $\chi^2 = 12.21$, $P = 0.002$), and cardiovascular disease (4 % vs. 9 % vs. 0 %, respectively; $\chi^2 = 6.24$, $P = 0.019$). Regarding the neuropsychological evaluation, significant differences in global cognition (28.1 ± 1.8 vs. 28.3 ± 1.7 vs. 29.0 ± 1.1; F = 5.22, $P = 0.007$), verbal memory (4.1 ± 1.5 vs. 5.1 ± 1.8 vs. 5.8 ± 1.7; F = 10.95, $P < 0.001$), semantic fluency (14.7 ± 4.5 vs. 17.1 ± 5.0 vs. 19.1 ± 5.4; F = 7.35, $P = 0.001$), depression (9.2 ± 6.5 vs. 9.5 ± 6.1 vs. 4.2 ± 3.4; F = 10.77, $P < 0.001$), and daily living activities (34.1 ± 2.7 vs. 33.7 ± 2.6 vs. 33.0 ± 0.2; F = 5.61, $P = 0.005$) were also observed between the groups. Interestingly, the SCDp group was older and performed worse on the verbal memory and semantic fluency tests at baseline than the participants of the HC and SCDnp groups (Table 2).

3.2. GM volumetric differences

3.2.1. VBM analysis

Compared with the HC group, SCD group showed significant decrease in GM volume in the frontal lobule, including the orbitofrontal (right rectal gyrus and left and right superior orbital gyri), frontal medial (left superior medial gyrus), and dorsolateral (left and right middle and superior frontal gyri) cortices; in the occipital lobule, including left and right calcarine gyrus, right inferior occipital gyrus, left superior occipital gyrus, left lingual gyrus, and left middle occipital gyrus; in both thalami; and in the anterior lobe of the cerebellum. Interestingly, the precuneus, which is a vulnerable region in AD, also exhibited reduced GM volume. However, no differences in other structures, such as the MTL, were noted between the groups (see Fig. 1 and Supplementary Table 4 for peak coordinates of these areas).

Comparison between the SCDnp and HC groups at baseline revealed

Table 1
Sociodemographic, clinical, and neuropsychological characteristics of the population included in the study.

	Controls (n = 43)	SCD (n = 309)	Stat (t or χ^2)	*P* value
Age at diagnosis, years	68.5 ± 6.0	65.4 ± 9.4	2.11	**<0.001**
Sex, women (%)	18 (41.9)	155 (50.2)	1.04	0.31
Education, years	9.8 ± 2.7	11.8 ± 3.3	−3.77	**<0.001**
Hypertension (%)	20 (46.5)	148 (48.2)	0.04	0.83
Diabetes mellitus (%)	0 (0)	41 (13.3)	6.46	**0.011**
Hypercholesterolemia (%)	15 (34.9)	176 (57.0)	7.41	**0.006**
Smoking (%)	6 (13.9)	105 (34)	7.01	**0.008**
Cerebrovascular disease (%)	1 (2.3)	11 (3.6)	0.17	1.000
Cardiovascular disease (%)	0 (0)	27 (8.7)	4.07	**0.044**
IDDD	33.0 ± 0	33.7 ± 2.7	1.92	0.055
GDS	4.2 ± 3.4	9.7 ± 6.4	5.32	**<0.001**
MMSE	29.0 ± 1.1	28.3 ± 1.8	−3.48	**<0.001**
Visual memory				
Figure recall 1	6.8 ± 3.8	6.5 ± 3.7	−0.86	0.390
Figure recall 2	6.2 ± 3	5.8 ± 3.2	−1.03	0.302
Verbal memory				
CERAD, delayed recall	5.8 ± 1.7	5.1 ± 1.8	−3.75	**<0.001**
Language				
BNT	49.6 ± 6.2	51.3 ± 4.4	0.59	0.554
Animals, score	19.1 ± 5.4	16.9 ± 5.2	−3.53	**<0.001**
Attention/executive functioning				
Stroop: total	41.5 ± 7.2	44.2 ± 6.1	1.34	0.182
TMT-A, seconds	57.2 ± 27.7	47.4 ± 25.9	−1.37	0.173
TMT-B, seconds	131.3 ± 66.0	114.2 ± 63.8	−0.01	0.991
Letter "p" score	14.2 ± 5.1	13.5 ± 5.0	−2.19	**0.029**
WML burden				
Lesion number[a]	9 (5, 14)	9 (4, 15)	−0.94	0.345
Total lesion volume (cm^3)[a]	1.07 (0.38, 3.65)	0.94 (0.22, 3.22)	1.42	0.156

Continuous variables are expressed as mean ± standard deviation, unless otherwise mentioned. Analysis of cognitive variables was adjusted for age, sex, and education. Differences in WML volume and lesion number were adjusted for age, sex, education, and scanner type.
[a]Variables are expressed in median (first quartile, third quartile).
BNT: Boston Naming Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; GDS: Geriatric Depression Rating Scale; IDDD, Interview for Deterioration in Daily Living; MMSE: Mini-Mental Examination; SCD: subjective cognitive decline; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WML: white matter lesion.

a similar pattern of GM volume decrease compared to that described previously, although it was more circumscribed and did not affect the precuneus (Fig. 2a and Supplementary Table 5 for peak coordinates of these areas). Among those who showed objective clinical decline during follow-up (SCDp) relative to HCs, the decrease in GM volume at baseline was limited to the frontal cortex, including the left and right superior frontal gyrus, middle frontal gyrus, superior orbital gyrus, middle orbital gyrus, right superior medial gyrus, and right rectal gyrus (see Fig. 2b and Supplementary Table 6 for peak coordinates of these areas). Interestingly, a comparison of the SCDp and SCDnp groups revealed a significant reduction in GM volume in both MTL (amygdala and left parahippocampal gyrus) in those who subsequently developed clinical progression (see Fig. 2c and Supplementary Table 7 for peak coordinates of these areas).

3.2.2. ROI analysis

ROI analysis revealed that compared to the HC group, the SCD group had decreased GM volume in the frontal lobe, including the orbitofrontal cortex (left rectal gyrus [$P = 0.000212$], left and right medial orbital gyri [$P = 0.0001$ and 0.000043, respectively]), the dorsolateral cortex (left and right middle frontal gyri [$P = 0.00015$ and 0.0003, respectively], and left and right superior frontal gyri [$P = 0.00021$ and 0.000013, respectively]). Occipital lobe atrophy was observed in the left and right calcarine fissure ($P = 0.00039$ and 0.00038, respectively), left thalamus ($P = 0.000064$), and right inferior parietal lobule (right angular gyrus; $P = 0.00033$).

Post hoc Bonferroni analyses compared the HC group to SCDp group and the SCDnp group to SCDp group, which revealed that those who progressed to MCI or dementia due to AD showed atrophy in four ROIs located in both MTL, corresponding to the left hippocampus and amygdala ($P = 0.00006$ and 0.00003, respectively) and the right hippocampus and amygdala ($P = 0.000074$ and 0.00018, respectively). No significant differences in the GM volume were observed between the HC and SCDnp groups.

3.3. WM group differences

3.3.1. VBM analysis

Compared to the HC group, patients with SCD showed anatomically reduced WM volume in different tracts, including the uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus, anterior thalamic radiation, and the major and minor callosum forceps, bilaterally (see Fig. 3 and Supplementary Fig. 2 and Supplementary Table 8 for peak coordinates of these areas and Supplementary Table 9 for total voxels size in cluster using XTRACT ATLAS). Multiple comparisons showed no significant differences in WM volume between the HC, SCDnp, and SCDp groups.

3.3.2. WML burden

Comparison between the SCD and HC groups showed no differences in the WML (SCD lesion number = 9 [median], interquartile range (IQR), 4–15; $P = 0.345$; SCD total lesion volume = 0.94 cm^3, IQR, 0.22–3.22; $P = 0.156$). Moreover, multiple comparisons between the SCDnp, SCDp, and HC groups showed no differences in the WML (SCDp lesion number = 11 [median], IQR, 7.5–16; $P = 0.468$; SCDp total lesion volume = 1.56 cm^3, IQR, 0.56–4.66; $P = 0.513$) (Tables 1 and 2).

4. Discussion

The current study revealed that participants with SCD showed significant brain structural changes measured on MRI compared with controls. First, VBM analysis revealed that SCD participants showed GM atrophy in the middle frontal gyri, superior orbital gyri, superior frontal gyri, right rectal gyrus, whole occipital lobule, and both thalami and precunei. Second, VBM analysis also found a decrease in WM volume in participants with SCD, affecting the uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus, anterior thalamic radiation, and callosum forceps. Third, ROI analysis demonstrated a decrease in GM volume in the left rectal gyrus, both medial orbital gyri, middle frontal gyri, superior frontal gyri, calcarine fissure, and left thalamus in participants with SCD. Fourth, the SCDp group showed greater baseline MTL atrophy than the SCDnp and HC groups on ROI analyses. However, the SCDp group showed an increase in baseline MTL atrophy only when compared to the SCDnp group on VBM. Fifth, no significant differences in WML burden were observed between the SCD and HC groups.

4.1. GM changes in the SCD

Structural neuroimaging studies on SCD samples have reported heterogeneous findings (Wang et al., 2020; Arrondo et al., 2022; Barkhof and Scheltens, 2002; Rivas-Fernández et al., 2023; Hafkemeijer et al., 2013). Our results revealed no significant difference in MTL volume reduction between the SCD and HC groups. In addition, the prefrontal cortex, occipital regions, precuneus, and thalamus were severely affected when assessed using ROI and VBM. Studies that applied ROI analytical methodology have mainly reported hippocampus and amygdala atrophy; however, the most studied region has been the MTL (Arrondo et al., 2022; Zajac et al., 2020). Recently, in a recent review by

Table 2
Clinical and neuropsychological characteristics of the population with follow-up.

	Control (n = 43)	**SCD non-progressors** (n = 67)	**SCD progressors** (n = 32)	**Stat (F or χ^2)**	***P* value**	**Group differences**
Age at diagnosis, years	68.5 ± 6.0	64.9 ± 8.3	71.0 ± 5.8	8.76	**<0.001**	SCDnp < C < SCDp
Follow-up time, months	15.7 ± 5.6	48.2 ± 37.8	58.6 ± 41.1	5.12	**<0.001**	C < SCDnp = SCDp
Sex, women (%)	18 (41.9)	36 (53.7)	12 (37.5)	2.82	0.244	NS
Education, years	9.8 ± 2.6	11.4 ± 3.3	12.7 ± 3.4	8.30	**<0.001**	C < SCDnp = SCDp
Hypertension (%)	20 (46.5)	30 (44.8)	20 (62.5)	2.91	0.233	NS
Diabetes mellitus (%)	0 (0)	9 (13.4)	3 (9.4)	6.15	0.046	C < SCDnp = SCDp
Hypercholesterolemia (%)	15 (34.9)	38 (57)	24 (75)	12.21	**0.002**	C < SCDnp = SCDp
Smoking (%)	6 (13.9)	18 (26.9)	10 (31.2)	3.61	0.154	NS
Cerebrovascular disease (%)	1 (2.3)	3 (4.5)	2 (6.2)	0.72	0.762	NS
Cardiovascular disease (%)	0 (0)	9 (13.4)	4 (12.5)	6.24	**0.019**	C < SCDnp = SCDp
MMSE	29.0 ± 1.1	28.3 ± 1.7	28.1 ± 1.8	5.22	**0.007**	C > SCDnp = SCDp
IDDD	33.0 ± 0.2	33.7 ± 2.6	34.1 ± 2.7	5.61	**0.005**	C < SCDnp = SCDp
GDS	4.2 ± 3.4	9.5 ± 6.1	9.2 ± 6.5	10.77	**<0.001**	C < SCDnp = SCDp
Visual memory						
Figure recall 1	6.8 ± 3.8	6.5 ± 3.7	5.5 ± 3.1	0.91	0.404	NS
Figure recall 2	6.2 ± 3	6.0 ± 3.2	5.7 ± 3.1	0.26	0.772	NS
Verbal memory						
CERAD, delayed recall	5.8 ± 1.7	5. 1 ± 1.8	4.1 ± 1.5	10.95	**<0.001**	C > SCDnp > SCDp
Language						
BNT	49.6 ± 6.2	50.6 ± 4.3	49.5 ± 4.4	0.45	0.640	NS
Animals, score	19.1 ± 5.4	17.1 ± 5.0	14.7 ± 4.5	7.35	**0.001**	C > SCDnp > SCDp
Attention/Executive Functioning						
Stroop: total	41.5 ± 7.2	44.8 ± 6.2	41.9 ± 6.1	2.54	0.08	NS
TMT-A, seconds	57.2 ± 27.7	44.8 ± 25.8	50.8 ± 25.3	2.77	0.066	NS
TMT-B, seconds	131.3 ± 66.0	117.5 ± 63.1	141.1 ± 64.1	1.49	0.229	NS
Letter "p" score	14.2 ± 5.1	12.8 ± 5.0	12.4 ± 5.0	3.04	0.051	NS
WML burden						
Lesion number[a]	9 (5, 14)	11 (4, 16)	11 (7.5, 16)	0.76	0.468	NS
Total lesion volume (cm^3)[a]	1.07 (0.38, 3.65)	1.06 (0.33, 2.92)	1.56 (0.57, 4.66)	0.67	0.513	NS

Continuous variables are expressed as mean ± standard deviation, unless otherwise mentioned. Analysis of cognitive variables was adjusted for age, sex and education. Differences on WML volume and lesion number were adjusted for age, sex, education and scanner type.
[a]Variables are expressed in median (first quartile, third quartile).
BNT: Boston Naming Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; GDS: Geriatric Depression Rating Scale; IDDD, Interview for Deterioration in Daily Living; MMSE: Mini-Mental Examination; NS: not significant; SCD: subjective cognitive decline; SCDnp: subjective cognitive decline non-progressor; SCDp: subjective cognitive decline progressor; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WML: white matter lesion

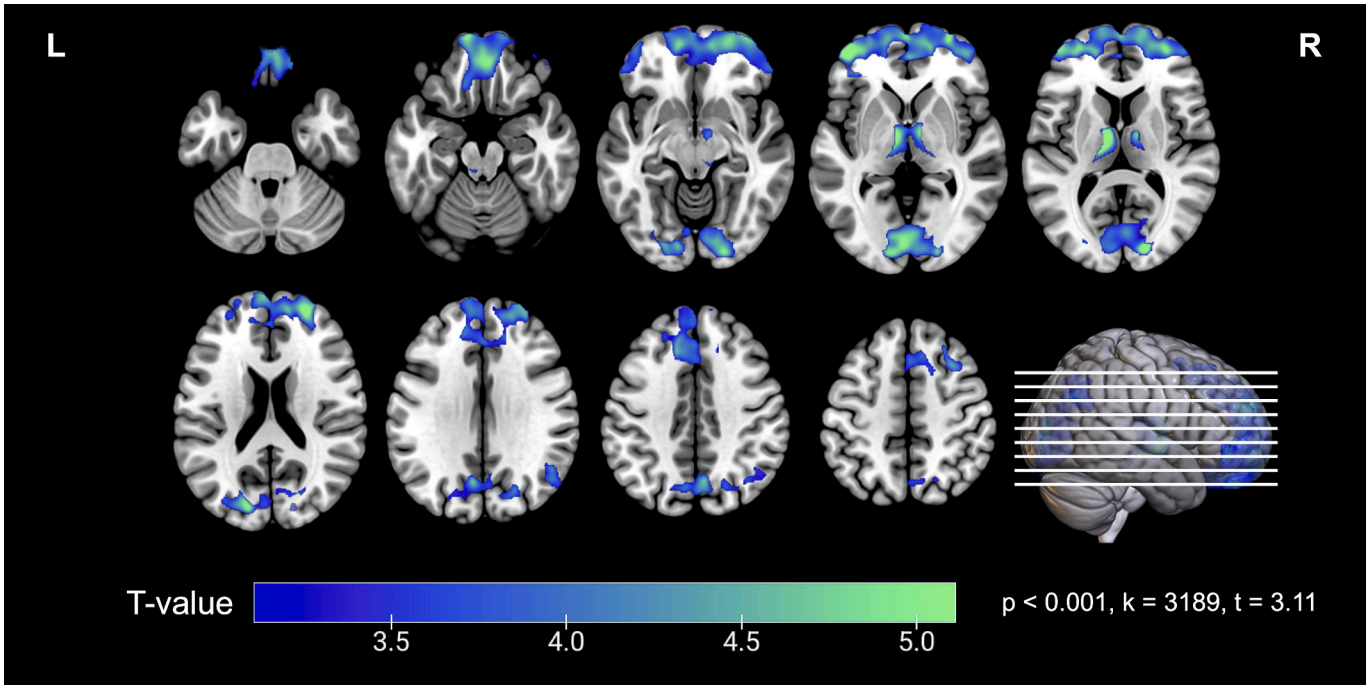

Fig. 1. Gray matter (GM) changes in participants with subjective cognitive decline (SCD) and healthy controls (HCs). SPM maps showing regions of decreased GM volume in the SCD group compared with the control group ($P < 0.05$ FWE cluster corrected) overlaid on anatomical T1-weighted images. Age, sex, education level, scanner type, and intracranial volume were included as covariates in the statistical model. Color scale shows the T-values. L = Left, R = Right.

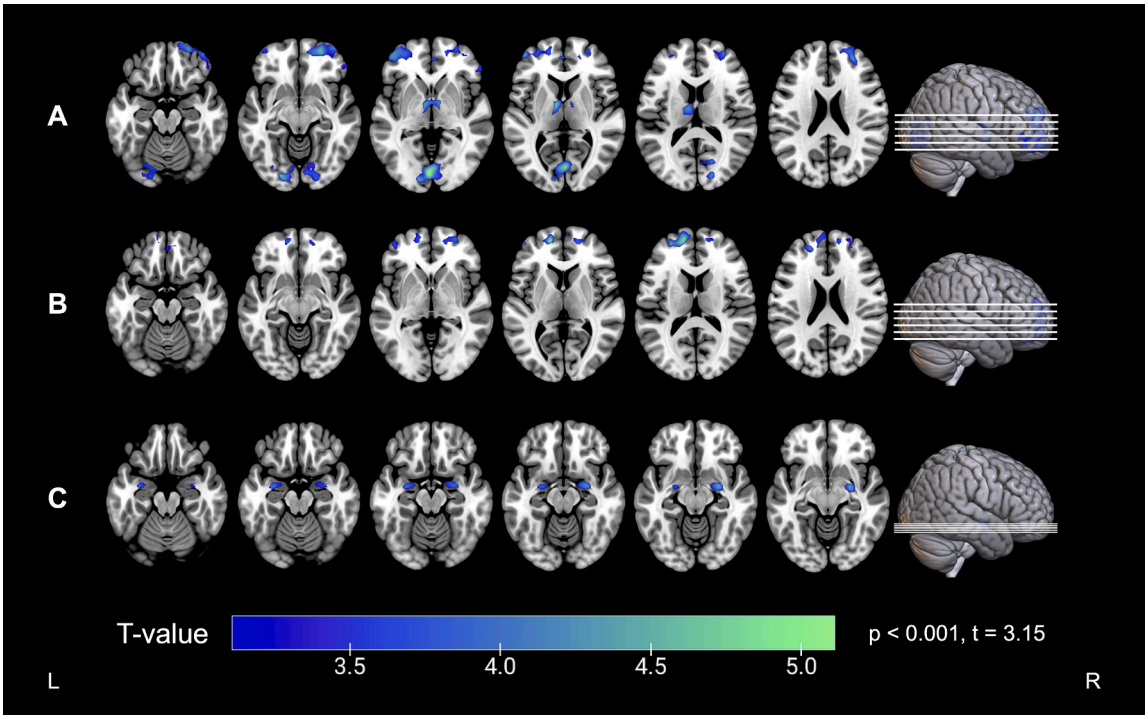

Fig. 2. Gray matter (GM) changes among participants with subjective cognitive decline who did (SCDp) and did not exhibit clinical progression (SCDnp). SPM maps overlaid on anatomical T1-weighted images comparing the regions in which GM volume decreased between (a) the SCDnp and control groups ($P < 0.05$ FWE cluster corrected), (b) the SCDp and control groups ($P < 0.05$ FWE cluster corrected), and (c) the SCDp and SCDnp groups ($P < 0.001$ FWE uncorrected). Age, sex, education level, scanner type, and intracranial volume were included as covariates in the statistical model. Color scale shows the T-values. L = Left, R = Right.

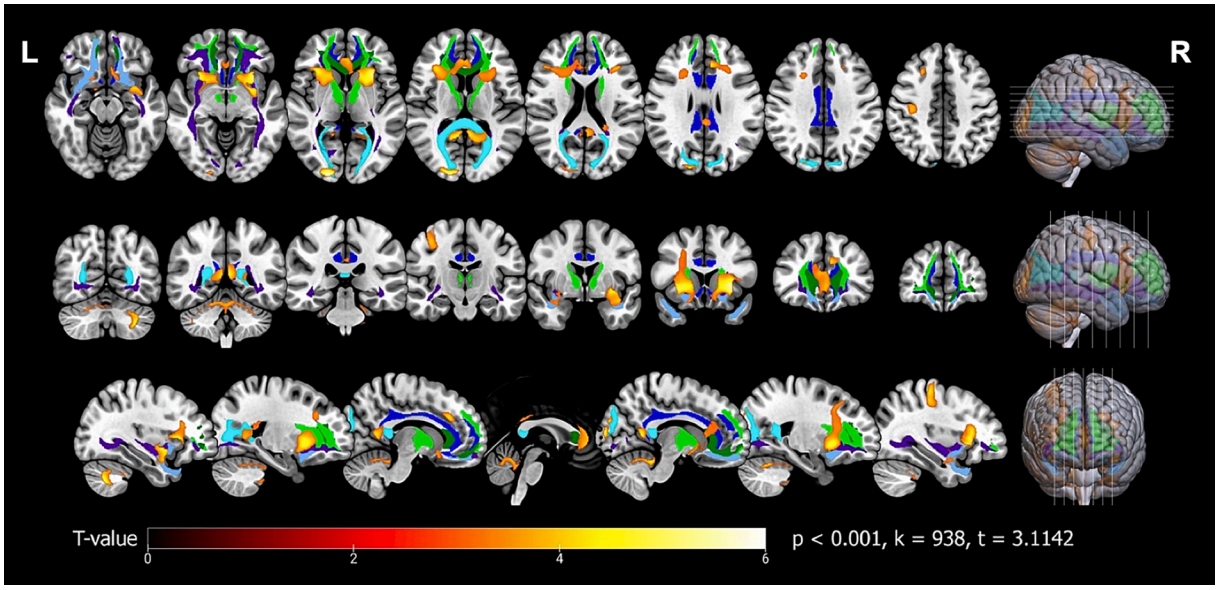

Fig. 3. White matter (WM) changes in subjective cognitive decline (SCD) and healthy control (HC) groups. SPM maps overlaid on anatomical images and XTRACT atlas comparing the regions in which WM volume decreased between the SCD and control groups ($P < 0.05$ FWE cluster corrected). Age, sex, education level, scanner type, and intracranial volume were included as covariates in the statistical model. Map color definitions: cyan = forceps minor; dark blue = cinguli; dark green = forceps major; light blue = uncinate fasciculi; light green = both anterior thalamic radiations; purple = inferior fronto-occipital fasciculi. L = Left, R = Right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Arrondo et al. (Arrondo et al., 2022) inconsistent structural changes between participants with SCD and HCs using different imaging analysis methods were observed. Overall, they found that the MTL was the most frequently affected area; however, the frontal and occipital lobes were also affected, albeit less frequently, and at least half of the studies found no significant differences between participants with SCD and HCs. These findings are consistent with another review conducted by Wang et al. (Wang et al., 2020) who also found that some studies repeatedly showed a decreased in hippocampal volume and GM networks disruptions.

Nonetheless, our imaging data showed that the SCDp group had lower GM volume in the MTL (hippocampus and amygdala) than the HC and SCDnp groups on ROI analysis. However, VBM analysis showed a

decrease in GM volume only in the SCDp group when compared to the SCDnp group, with a VBM comparison between the HC and SCDp groups showing volume loss circumscribed to the frontal lobes. Our findings are consistent with those reported in previous studies, which showed a strong association between lower hippocampal volume and cognitive decline progression (Ebenau et al., 2022; Stewart et al., 2008). The diversity of these findings could be attributed to the variability in the conceptualization and operationalization of the clinical syndrome (Molinuevo et al., 2017); differences in neuroimaging acquisition and methodological analyses, such as manual, semi-automatic, and automatic segmentation applied in ROI analyses (Arrondo et al., 2022); and variations in demographic features, sample size, and participant recruitment across different research environments, such as population-based cohorts, volunteer samples, or patients from clinical settings (Rabin et al., 2017; Wang et al., 2020; Jessen et al., 2023). In addition, automated ROI analysis has been reported to be at a relative disadvantage when compared with VBM, given the "dilution of the effect" in small-scale GM deficits (Voormolen et al., 2010).

Currently, evidence has shown that GM loss in the prefrontal cortex leads to poor judgment, planning, and decision-making (Miller, 2000; Funahashi, 2017). Moreover, interactions between the prefrontal cortex, thalamus, and hippocampus modulate cognitive processing, episodic memory, and behavior (Fuster, 2015; Jagirdar and Chin, 2019; Chao et al., 2020). Some researchers have found that patients with SCD exhibit atrophy across different regions of the frontal lobe, including the prefrontal cortex, when compared to HCs (Hafkemeijer et al., 2013; Saykin et al., 2006), with such findings being consistent with our results. Nevertheless, subjects with SCD whose disease later progressed to MCI or dementia showed GM volume loss in the hippocampus and amygdala. Li et al. (Li et al., 2023) found that hippocampal atrophy in patients with SCD increases the risk of progression to cognitive impairment by 54 %. Therefore, measurements of hippocampal volumes could be useful in the diagnosis of early AD (Laakso et al., 1995). Our findings support the contention that patients with SCD exhibit subtle impairment involving executive and higher cognitive functions, which is not objectified by current cognitive tests (Chen et al., 2020). These data are associated with the etiological heterogeneity of the clinical syndrome given that the frontal lobe, despite its relationship with executive functions and working memory, is not typically affected in the early stages of AD (Arrondo et al., 2022; Braak and Braak, 1991).

Studies have shown that patients with early-onset AD have lower precuneus GM density (Karas et al., 2007; Sakamoto et al., 2002). The precuneus is well known for its role in audiovisual multisensory processes, sustained attention, episodic memory retrieval, and self-consciousness while forming part of the default-mode network (Molholm et al., 2006; Pardo et al., 1991; Fletcher et al., 1995; Utevsky et al., 2014; Cavanna and Trimble, 2006). Previous studies have found that patients with SCD had a significantly smaller precuneus than those with HCs, albeit with preserved hippocampal volume (Choi et al., 2015). Interestingly, our study showed that the SCD group exhibited significant atrophy in both precunei. These data show SCD as the earliest manifestation of AD (Scheef et al., 2012). Furthermore, both thalami were smaller in patients with SCD than in HCs, although Hafkemeijer et al. (Hafkemeijer et al., 2013) found no significant atrophy in the thalamus.

Visual processing, visuospatial integration, and spatial memory are associated with the occipital cortex (Chen et al., 2020; Shao et al., 2018; Sulpizio et al., 2013). Although patients with SCD, in our study, showed occipital atrophy, it was not significant in those whose disease progressed. Previous studies have described a significant loss in occipital lobe volume in patients with SCD (Hafkemeijer et al., 2013), whereas other studies highlight the relationship between vision impairment and early signs of cognitive decline (Chen et al., 2020; Fujimori et al., 1998; Saydah et al., 2019; Chan et al., 2019).

Overall, through different analytical methodologies, studies have reported that patients with SCD, both at baseline and during longitudinal follow-up, exhibited a decrease in the total hippocampal volume within the same regions described in AD (Wang et al., 2020; Arrondo et al., 2022; Braak and Braak, 1991; Perrotin et al., 2015). As such, consistent changes in MTL could be associated with subsequent progression of cognitive impairment.

4.2. WM changes in SCD

Considering the high soft tissue resolution of MRI (Chen et al., 2023), the current study analyzed T1-weighted images using a voxel-based analysis of anatomical MRI and overlay regions of WM atrophy on WM tract maps generated using an XTRACT atlas tool to determine differences in WM pathways between patients with SCD and HCs. However, WM microstructural abnormalities and network activity can be observed more effectively with diffusion MRI, which has been widely employed in patients with SCD to assess the integrity of WM tissues (Chen et al., 2023). In terms of WM disruption, our results were consistent with those presented in previous studies, which showed that the differences between participants with SCD and HCs comprised the major and minor forceps, both cingulum, anterior thalamic radiation, uncinate fasciculus, and inferior fronto-occipital fasciculus (Chen et al., 2023; Li et al., 2016; Ohlhauser et al., 2019; Luo et al., 2019). In addition, studies have observed correlations between WM impairment and global cognitive, lower executive functions, and memory decline (Ohlhauser et al., 2019; Luo et al., 2019). Importantly, these impaired tracts connect the earliest affected GM structures in MCI and AD (Luo et al., 2019; Wen et al., 2019). The corpus callosum is involved in information transfer between cerebral hemispheres, learning, memory, cognition, 3D visual capacity, executive functions, and visual reaction time (Huang et al., 2015). The uncinate fasciculus is a bidirectional WM tract that connects the lateral orbitofrontal cortex with the temporal lobe; moreover, its function is related to memory processes (Von Der Heide et al., 2013). The anterior thalamic radiation connects the thalamus to the frontal lobe, and the superior longitudinal fasciculus projects from the frontal lobe to the temporal, parietal, and occipital lobes (Liang et al., 2021).

Our study demonstrated that patients with SCD had widespread loss of WM pathway integrity in regions similar to those determined in diffusion MRI studies. Nevertheless, insufficient evidence is available to correlate our findings of WM tract impairment on structural MRI with microstructural changes determined through diffusion MRI, given that the latter could be more sensitive than anatomical imaging. However, we noted that GM atrophy and WM disruptions are anatomically correlated in patients with SCD. These findings are consistent with those reported in previous studies, which further found that WM degeneration was similar to those observed in MCI and dementia due to AD (Liang et al., 2021; Wen et al., 2019). This structural degeneration reinforces the notion that widespread brain damage may precede objectively measurable memory decline and involves a distributed degeneration process (Selnes et al., 2012; Ohlhauser et al., 2019; Luo et al., 2019).

4.3. WML burden in SCD

WMLs represent increased and altered water content in hydrophobic WM tracts caused by pathological processes, including neuroinflammation, demyelination, and axonal loss (Bahsoun et al., 2022). These lesions are prevalent on MRI scans of aging brains and are part of cerebral small vessel disease (Wardlaw et al., 2013). Suppression of the cerebrospinal fluid in T2-w FLAIR MRI improves the visibility of WMLs and better distinguishes between WMLs and Virchow–Robin spaces and lacunes (Barkhof and Scheltens, 2002). The mechanisms underlying the occurrence of WML with neurodegeneration and the development of cognitive impairment are yet to be fully understood (Caillaud et al., 2020). Vascular risk factors have been linked to the development of WML and imply an increased risk of cognitive impairment and dementia (Lam et al., 2017; Caillaud et al., 2020; Kivipelto et al., 2001; Vuorinen et al., 2011). Ashrafi et al. (Ashrafi et al., 2019) found a correlation

between total WML volume and decreased cognitive function in a population without memory complaints but with cardiovascular risk factors. Meanwhile, van Rooden et al. (van Rooden et al., 2018) found that increased WML volumes were a predictor of memory complaints patients with SCD, suggesting that vascular damage could be an early marker of early-stage AD. Consistent with these findings, Bahsoun et al. (Bahsoun et al., 2022) suggested that normal-appearing WM changes precede WMLs. In addition, severe WMLs frequently coexist with MTL and global brain atrophy (den Heijer et al., 2005).

Burns et al (Burns et al., 2005). reported that individuals with SCD may be more vulnerable to the effects of WMLs on cognition than individuals without cognitive complaints with a similar WML burden. De Groot et al. (De Groot et al., 2002) revealed that the severity of periventricular, but not subcortical WML, in older adults without dementia was associated with the rate of cognitive decline. However, the location of the WML had a more significant impact on cognition than total load measurement (Bahsoun et al., 2022). This study showed that participants with SCD exhibited significantly more vascular risk factors, such as diabetes mellitus, hypercholesterolemia, smoking habit, and cardiovascular disease, than HCs and had significantly greater WM damage. However, no differences in WML load were found between participants with SCD and HC or patients who showed clinical progression. These findings may be attributed to several factors, such as the methodology used, because we measured the total WML load without identifying the location. Moreover, the imaging acquisition technique could be improved to detect WML using 3D FLAIR sequences (Paniagua Bravo et al., 2014), and the criteria for defining SCD may also be associated with the heterogeneity of the results, although some studies have found an association between WML burden and worsening cognition in healthy populations (Caillaud et al., 2020; Ashrafi et al., 2019).

Although this study was performed using a large memory center sample of patients with SCD, the number of samples evaluated to determine clinical progression in the subgroups was small. Additionally, four types of studies were performed on the same sample, including 120 ROIs during analysis. Nevertheless, some limitations of our study must be noted. First, the current research was a retrospective database analysis, which precluded a more homogeneous sample selection or the performance of a prospective longitudinal follow-up on the total SCD sample owing to data unavailability. Second, patients were scanned using two different 1.5-T MRI scanners under different parameters, which may have affected our results. However, sex, age, education level, scanner type, and total intracranial volume were included as covariates during analyses. Third, the HC group was smaller in size than the SCD group and had different medical and demographic conditions, which may have caused bias due to the lack of knowledge regarding factors present as biomarkers of amyloidosis, tau burden, or APOEε4 carriers (Rabin et al., 2017). Fourth, patients whose disease progressed to another stage of cognitive impairment did not undergo brain MRI during follow-up, although a neuropsychological follow-up was performed. Therefore, the longitudinal follow-up was only used to determine clinical progression and not changes in MRI findings. Fifth, although WM tract analysis was performed using VBM, diffusion MRI analysis was not performed despite the similar findings. Sixth, although T2-weighted 2D FLAIR sequences were used to quantify WML, 3D FLAIR sequences could facilitate the detection of small WML (Paniagua Bravo et al., 2014).

In conclusion, participants with SCD exhibited reduced GM volume in the frontal lobe, occipital lobe, precunei, and thalami. MTL atrophy was observed on baseline MRI among patients with SCD who experienced clinical disease progression. These findings support the initial heterogeneity of the syndrome and reinforce previous knowledge suggesting that structural damage in the hippocampus and amygdalae would have already begun during the long presymptomatic period of AD. Moreover, the affected GM regions in the cerebral cortex were anatomically correlated with the impaired WM tracts in patients with SCD. Although numerous studies have reported a relationship between WML and cognitive decline, no significant differences were observed in our sample. Hence, future longitudinal studies with larger samples of patients with SCD-plus, which includes more features probably observed in preclinical AD, are needed to assess the cognitive trajectory of subjects who exhibit cognitive impairment progression.

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CRediT authorship contribution statement

Mario Riverol: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis. **Mirla M. Ríos-Rivera:** Writing – original draft, Investigation, Data curation. **Laura Imaz-Aguayo:** Formal analysis, Data curation. **Sergio M. Solis-Barquero:** Formal analysis. **Carlota Arrondo:** Formal analysis, Data curation. **Genoveva Montoya-Murillo:** Formal analysis, Data curation. **Rafael Villino-Rodríguez:** Formal analysis, Data curation. **Reyes García-Eulate:** Formal analysis. **Pablo Domínguez:** Formal analysis. **Maria A. Fernández-Seara:** Validation, Supervision, Software, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103615.

References

Albert, M.S., DeKosky, S.T., Dickson, D., et al., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Arrondo, P., Elía-Zudaire, Ó., Martí-Andrés, G., Fernández-Seara, M.A., Riverol, M., 2022. Grey matter changes on brain MRI in subjective cognitive decline: a systematic review. Alzheimers Res Ther. 14, 98. https://doi.org/10.1186/s13195-022-01031-6.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage. 38, 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage. 26, 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018.

Ashrafi, F., Taheri, M.S., Farzaneh, A., Behnam, B., Ahmadi, M.A., 2019. Cognitive functions and white matter lesions on magnetic resonance images in a sample of normal Iranian population with cardiovascular risk factors. Neuroradiol J. 32, 108–114. https://doi.org/10.1177/1971400919825862.

Bahsoun, M.A., Khan, M.U., Mitha, S., et al., 2022. FLAIR MRI biomarkers of the normal appearing brain matter are related to cognition. NeuroImage Clin. 34, 102955 https://doi.org/10.1016/j.nicl.2022.102955.

Barkhof, F., Scheltens, P., 2002. Imaging of white matter lesions. Cerebrovasc Dis. 13 (Suppl 2), 21–30. https://doi.org/10.1159/000049146.

Benedictus, M.R., van Harten, A.C., Leeuwis, A.E., et al., 2015. White matter hyperintensities relate to clinical progression in subjective cognitive decline. Stroke. 46, 2661–2664. https://doi.org/10.1161/STROKEAHA.115.009475.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259. https://doi.org/10.1007/BF00308809.

Burns, J.M., Church, J.A., Johnson, D.K., et al., 2005. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. Arch Neurol. 62 (12), 1870–1876. https://doi.org/10.1001/archneur.62.12.1870.

Caillaud, M., Hudon, C., Boller, B., et al., 2020. Evidence of a relation between hippocampal volume, white matter hyperintensities, and cognition in subjective cognitive decline and mild cognitive impairment. J Gerontol B Psychol Sci Soc Sci. 75, 1382–1392. https://doi.org/10.1093/geronb/gbz120.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain. 129, 564–583. https://doi.org/10.1093/brain/awl004.
Chan, V.T.T., Sun, Z., Tang, S., et al., 2019. Spectral-domain OCT measurements in Alzheimer's disease: A systematic review and meta-analysis. Ophthalmology. 126, 497–510. https://doi.org/10.1016/j.ophtha.2018.08.009.
Chao, O.Y., de Souza Silva, M.A., Yang, Y.M., Huston, J.P., 2020. The medial prefrontal cortex - hippocampus circuit that integrates information of object, place and time to construct episodic memory in rodents: behavioral, anatomical and neurochemical properties. Neurosci Biobehav Rev. 113, 373–407. https://doi.org/10.1016/j.neubiorev.2020.04.007.
Chen, Y., Wang, Y., Song, Z., Fan, Y., Gao, T., Tang, X., 2023. Abnormal white matter changes in Alzheimer's disease based on diffusion tensor imaging: A systematic review. Ageing Res Rev. 87, 101911 https://doi.org/10.1016/j.arr.2023.101911.
Chen, S., Xu, W., Xue, C., et al., 2020. Voxelwise meta-analysis of gray matter abnormalities in mild cognitive impairment and subjective cognitive decline using activation likelihood estimation. J Alzheimers Dis. 77, 1495–1512. https://doi.org/10.3233/JAD-200659.
Choi, Y., Yoon, B.-N., Choi, S.H., Lim, M.K., Kim, H.-J., Yang, D.-W., 2015. Reduced gray matter volume in subjective cognitive decline: a voxel-based morphometric study. Dement Neurocognitive Disord. 14, 143. https://doi.org/10.12779/DND.2015.14.4.143.
De Groot, J.C., De Leeuw, F.E., Oudkerk, M., et al., 2002. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol. 52 (3), 335–341. https://doi.org/10.1002/ana.10294.
den Heijer, T., Launer, L.J., Prins, N.D., et al., 2005. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology. 64 (2), 263–267. https://doi.org/10.1212/01.WNL.0000149641.55751.2E.
Dong, G., Yang, L., Li, C.R., et al., 2020. Dynamic network connectivity predicts subjective cognitive decline: the sino-longitudinal cognitive impairment and dementia study. Brain Imaging Behav. 14, 2692–2707. https://doi.org/10.1007/s11682-019-00220-6.
Dubois, B., Feldman, H.H., Jacova, C., et al., 2014. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 13, 614–629. https://doi.org/10.1016/S1474-4422(14)70090-0.
Ebenau, J.L., Pelkmans, W., Verberk, I.M.W., et al., 2022. Association of CSF, plasma, and imaging markers of neurodegeneration with clinical progression in people with subjective cognitive decline. Neurology. 98, e1315–e1326. https://doi.org/10.1212/WNL.0000000000200035.
Fletcher, P.C., Frith, C.D., Baker, S.C., Shallice, T., Frackowiak, R.S., Dolan, R.J., 1995. The mind's eye–precuneus activation in memory-related imagery. Neuroimage. 2, 195–200. https://doi.org/10.1006/nimg.1995.1025.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
Fujimori, M., Imamura, T., Yamashita, H., et al., 1998. Age at onset and visuocognitive disturbances in Alzheimer disease. Alzheimer Dis Assoc Disord. 12, 163–166. https://doi.org/10.1097/00002093-199809000-00007.
Funahashi, S., 2017. Working memory in the prefrontal cortex. Brain Sci. 7, 49. https://doi.org/10.3390/brainsci7050049.
Fuster, J.M., 2015. The Prefrontal Cortex, 5th ed. Academic Press, New York, NY.
Golden, C.J., 1978. Stroop Color and Word Test. Stoeling, Chicago, IL.
Gunning-Dixon, F.M., Raz, N., 2000. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology. 14, 224–232. https://doi.org/10.1037/0894-4105.14.2.224.
Hafkemeijer, A., Altmann-Schneider, I., Oleksik, A.M., et al., 2013. Increased functional connectivity and brain atrophy in elderly with subjective memory complaints. Brain Connect. 3, 353–362. https://doi.org/10.1089/brain.2013.0144.
Huang, X., Du, X., Song, H., et al., 2015. Cognitive impairments associated with corpus callosum infarction: a ten cases study. Int J Clin Exp Med. 8, 21991–21998.
Jack Jr, C.R., Bennett, D.A., Blennow, K., et al., 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14, 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.
Jagirdar, R., Chin, J., 2019. Corticothalamic network dysfunction and Alzheimer's disease. Brain Res. 1702, 38–45. https://doi.org/10.1016/j.brainres.2017.09.014.
Jessen, F., Amariglio, R.E., van Boxtel, M., et al., 2014. Subjective Cognitive Decline Initiative (SCD-I) Working Group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 10, 844–852. https://doi.org/10.1016/j.jalz.2014.01.001.
Jessen, F., Wolfsgruber, S., Kleineindam, L., et al., 2023. Subjective cognitive decline and stage 2 of Alzheimer disease in patients from memory centers. Alzheimers Dement. 19, 487–497. https://doi.org/10.1002/alz.12674.
Kaplan, E., Goodglass, H., Weintraub, S., 2001. The Boston Naming Test, 2nd ed. Lippincott Williams & Wilkins, Philadelphia, PA.
Karas, G., Scheltens, P., Rombouts, S., et al., 2007. Precuneus atrophy in early-onset Alzheimer's disease: a morphometric structural MRI study. Neuroradiology. 49, 967–976. https://doi.org/10.1007/s00234-007-0269-2.
Kivipelto, M., Helkala, E.L., Laakso, M.P., et al., 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population-based study. BMJ. 322, 1447–1451. https://doi.org/10.1136/bmj.322.7300.1447.
Laakso, M.P., Soininen, H., Partanen, K., et al., 1995. Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. J Neural Transm Park Dis Dement Sect. 9, 73–86. https://doi.org/10.1007/BF02252964.
Lam, C.L.M., Yiend, J., Lee, T.M.C., 2017. Imaging and neuropsychological correlates of white matter lesions in different subtypes of mild cognitive impairment: A systematic review. NeuroRehabilitation. 41, 189–204. https://doi.org/10.3233/NRE-171471.
Li, H., Tan, C.C., Tan, L., Xu, W., 2023. Predictors of cognitive deterioration in subjective cognitive decline: evidence from longitudinal studies and implications for SCD-plus criteria. J Neurol Neurosurg Psychiatry. 94, 844–854. https://doi.org/10.1136/jnnp-2022-330246.
Li, X.Y., Tang, Z.C., Sun, Y., Tian, J., Liu, Z.Y., Han, Y., 2016. White matter degeneration in subjective cognitive decline: a diffusion tensor imaging study. Oncotarget. 7, 54405–54414. https://doi.org/10.18632/oncotarget.10091.
Liang, L., Chen, Z., Wei, Y., et al., 2021. Fusion analysis of gray matter and white matter in subjective cognitive decline and mild cognitive impairment by multimodal CCA-joint ICA. NeuroImage Clin. 32, 102874 https://doi.org/10.1016/j.nicl.2021.102874.
Luo, C., Li, M., Qin, R., et al., 2019. White matter microstructural damage as an early sign of subjective cognitive decline. Front Aging Neurosci. 11, 378. https://doi.org/10.3389/fnagi.2019.00378.
McKhann, G.M., Knopman, D.S., Chertkow, H., et al., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.
Miller, E.K., 2000. The prefrontal cortex and cognitive control. Nat Rev Neurosci. 1, 59–65. https://doi.org/10.1038/35036228.
Molholm, S., Sehatpour, P., Mehta, A.D., et al., 2006. Audio-visual multisensory integration in superior parietal lobule revealed by human intracranial recordings. J Neurophysiol. 96, 721–729. https://doi.org/10.1152/jn.00285.2006.
Molinuevo, J.L., Rabin, L.A., Amariglio, R., et al., 2017. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement. 13, 296–311. https://doi.org/10.1016/j.jalz.2016.09.012.
Morris, J.C., Mohs, R.C., Rogers, H., Fillenbaum, G., Heyman, A., 1988. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. Psychopharmacol Bull. 24, 641–652.
Morrison, C., Dadar, M., Shafiee, N., Villeneuve, S., 2022. Louis Collins D, for Alzheimer's Disease Neuroimaging Initiative. Regional brain atrophy and cognitive decline depend on definition of subjective cognitive decline. NeuroImage Clin. 33, 102923 https://doi.org/10.1016/j.nicl.2021.102923.
Ohlhauser, L., Parker, A.F., Smart, C.M., Gawryluk, J.R., 2019. Alzheimer's Disease Neuroimaging Initiative. White matter and its relationship with cognition in subjective cognitive decline. Alzheimers Dement (amst) 11, 28–35. https://doi.org/10.1016/j.dadm.2018.10.008.
Paniagua Bravo Á, Sánchez Hernández JJ, Ibáñez Sanz L, Alba de Cáceres I, Crespo San José JL, García-Castaño Gandariaga B. A comparative MRI study for white matter hyperintensities detection: 2D-FLAIR, FSE PD 2D, 3D-FLAIR and FLAIR MIP. *Br J Radiol*. 2014;87(1035):20130360. doi:10.1259/bjr.20130360.
Pardo, J.V., Fox, P.T., Raichle, M.E., 1991. Localization of a human system for sustained attention by positron emission tomography. Nature. 349, 61–64. https://doi.org/10.1038/349061a0.
Perrotin, A., de Flores, R., Lamberton, F., et al., 2015. Hippocampal subfield volumetry and 3D surface mapping in subjective cognitive decline. J Alzheimers Dis. 48 (Suppl 1), S141–S150. https://doi.org/10.3233/JAD-150087.
Platero, C., López, M.E., Carmen Tobar, M.D., Yus, M., Maestu, F., 2019. Discriminating Alzheimer's disease progression using a new hippocampal marker from T_1-weighted MRI: the local surface roughness. Hum Brain Mapp 40, 1666–1676. https://doi.org/10.1002/hbm.24478.
Prins, N.D., Scheltens, P., 2015. White matter hyperintensities, cognitive impairment and dementia: an update. Nat Rev Neurol. 11, 157–165. https://doi.org/10.1038/nrneurol.2015.10.
Qi, X., Tang, H., Luo, Q., et al., 2019. White matter hyperintensities predict cognitive decline: A community-based study. Can J Neurol Sci. 46, 383–388. https://doi.org/10.1017/cjn.2019.47.
Rabin, L.A., Smart, C.M., Amariglio, R.E., 2017. Subjective cognitive decline in preclinical Alzheimer's disease. Annu Rev Clin Psychol. 13, 369–396. https://doi.org/10.1146/annurev-clinpsy-032816-045136.
Ramier, A.M., Hecaen, H., 1970. Role respectif des atteintes frontales et de la lateralisation lesionnelle dans les déficits de la fluence verbale. Rev Neurol. 132, 17–22.
Reitan, R.M., Wolfson, D., 1993. The Halstead-Reitan Neuropsychological Test Battery. Theory and Clinical Interpretation, 2nd ed. Neuropsychology Press, Tucson, AZ.
Rivas-Fernández, M.Á., Lindín, M., Zurrón, M., et al., 2023. Neuroanatomical and neurocognitive changes associated with subjective cognitive decline. Front Med (lausanne). 10, 1094799. https://doi.org/10.3389/fmed.2023.1094799.
Rodríguez-Gómez, O., Abdelnour, C., Jessen, F., Valero, S., Boada, M., 2015. Influence of sampling and recruitment methods in studies of subjective cognitive decline. J Alzheimers Dis. 48 (Suppl 1), S99–S107. https://doi.org/10.3233/JAD-150189.
Sakamoto, S., Ishii, K., Sasaki, M., et al., 2002. Differences in cerebral metabolic impairment between early and late onset types of Alzheimer's disease. J Neurol Sci. 200, 27–32. https://doi.org/10.1016/s0022-510x(02)00114-4.
Saydah, S., Gerzoff, R.B., Taylor, C.A., Ehrlich, J.R., Saaddine, J., 2019. Vision impairment and subjective cognitive decline-related functional limitations – United States, 2015–2017. MMWR Morb Mortal Wkly Rep. 68, 453–457. https://doi.org/10.15585/mmwr.mm6820a2.
Saykin, A.J., Wishart, H.A., Rabin, L.A., et al., 2006. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 67, 834–842. https://doi.org/10.1212/01.wnl.0000234032.77541.a2.

Scheef, L., Spottke, A., Daerr, M., et al., 2012. Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. Neurology. 79, 1332–1339. https://doi.org/10.1212/WNL.0b013e31826c1a8d.

Scheltens, P., Blennow, K., Breteler, M.M., et al., 2016. Alzheimer's disease. Lancet. 388, 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1.

P. Selnes A.M. Fjell L. Gjerstad et al. White matter imaging changes in subjective and mild cognitive impairment Alzheimers Dement. 2012 8(5);Suppl:S112–S121. 10.1016/j.jalz.2011.07.001.

Shao, Y., Bao, J., Huang, X., et al., 2018. Comparative study of interhemispheric functional connectivity in left eye monocular blindness versus right eye monocular blindness: a resting-state functional MRI study. Oncotarget. 9, 14285–14295. https://doi.org/10.18632/oncotarget.24487.

Sperling, R.A., Aisen, P.S., Beckett, L.A., et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

Stewart, R., Dufouil, C., Godin, O., et al., 2008. Neuroimaging correlates of subjective memory deficits in a community population. Neurology. 70, 1601–1607. https://doi.org/10.1212/01.wnl.0000310982.99438.54.

Sulpizio, V., Committeri, G., Lambrey, S., Berthoz, A., Galati, G., 2013. Selective role of lingual/parahippocampal gyrus and retrosplenial complex in spatial memory across viewpoint changes relative to the environmental reference frame. Behav Brain Res. 242, 62–75. https://doi.org/10.1016/j.bbr.2012.12.031.

Teunisse, S., Derix, M.M., van Crevel, H., 1991. Assessing the severity of dementia. Patient and Caregiver. *Arch Neurol.* 48, 274–277. https://doi.org/10.1001/archneur.1991.00530150042015.

Utevsky, A.V., Smith, D.V., Huettel, S.A., 2014. Precuneus is a functional core of the default-mode network. J Neurosci. 34, 932–940. https://doi.org/10.1523/JNEUROSCI.4227-13.2014.

van Rooden, S., van den Berg-Huysmans, A.A., Croll, P.H., et al., 2018. Subjective cognitive decline is associated with greater white matter hyperintensity volume. J Alzheimers Dis. 66, 1283–1294. https://doi.org/10.3233/JAD-180285.

Vogel, A., Salem, L.C., Andersen, B.B., Waldemar, G., 2016. Differences in quantitative methods for measuring subjective cognitive decline - results from a prospective memory clinic study. Int Psychogeriatr. 28 (9), 1513–1520. https://doi.org/10.1017/S1041610216000272.

Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain. 136, 1692–1707. https://doi.org/10.1093/brain/awt094.

Voormolen, E.H., Wei, C., Chow, E.W., Bassett, A.S., Mikulis, D.J., Crawley, A.P., 2010. Voxel-based morphometry and automated lobar volumetry: the trade-off between spatial scale and statistical correction. Neuroimage. 49, 587–596. https://doi.org/10.1016/j.neuroimage.2009.07.018.

Vuorinen, M., Solomon, A., Rovio, S., et al., 2011. Changes in vascular risk factors from midlife to late life and white matter lesions: a 20-year follow-up study. Dement Geriatr Cogn Disord. 31 (2), 119–125. https://doi.org/10.1159/000323810.

Wang, X., Huang, W., Su, L., et al., 2020. Neuroimaging advances regarding subjective cognitive decline in preclinical Alzheimer's disease. Mol Neurodegener. 15, 55. https://doi.org/10.1186/s13024-020-00395-3.

Wang, Y., West, J.D., Flashman, L.A., et al., 2012. Selective changes in white matter integrity in MCI and older adults with cognitive complaints. Biochim Biophys Acta. 1822, 423–430. https://doi.org/10.1016/j.bbadis.2011.08.002.

Wardlaw, J.M., Smith, C., Dichgans, M., 2013. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 12, 483–497. https://doi.org/10.1016/S1474-4422(13)70060-7.

Wen, Q., Mustafi, S.M., Li, J., et al., 2019. White matter alterations in early-stage Alzheimer's disease: A tract-specific study. Alzheimers Dement (amst). 11, 576–587. https://doi.org/10.1016/j.dadm.2019.06.003.

Woo, C.W., Krishnan, A., Wager, T.D., 2014. Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. Neuroimage. 91, 412–419. https://doi.org/10.1016/j.neuroimage.2013.12.058.

Yesavage, J.A., Brink, T.L., Rose, T.L., et al., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 17, 37–49. https://doi.org/10.1016/0022-3956(82)90033-4.

L. Zajac B.B. Koo Y. Tripodis et al. Hippocampal resting-state functional connectivity patterns are more closely associated with severity of subjective memory decline than whole hippocampal and subfield volumes Cereb Cortex Commun. 2020;1:tgaa019. 10.1093/texcom/tgaa019.