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Resting-state functional connectivity abnormalities in subjective cognitive decline: A 7T MRI study

M. Pievani [a,*], F. Ribaldi [b,c], K. Toussas [b], S. Da Costa [d], J. Jorge [e], O. Reynaud [d,f], C. Chicherio [c], J.L. Blouin [g], M. Scheffler [h], V. Garibotto [i,j,k], J. Jovicich [l], I.O. Jelescu [d,m], G.B. Frisoni [b,c]

[a] Laboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[b] Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland
[c] Geneva Memory Center, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland
[d] CIBM Center for Biomedical Imaging, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[e] CSEM – Swiss Center for Electronics and Microtechnology, Bern, Switzerland
[f] Fondation Campus Biotech Geneva, Geneva, Switzerland
[g] Genetic Medicine, Diagnostics Dept, University Hospitals and University of Geneva, Geneva, Switzerland
[h] Division of Radiology, Geneva University Hospitals, Geneva, Switzerland
[i] Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University Neurocenter and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[j] Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals, Geneva, Switzerland
[k] CIBM Center for Biomedical Imaging, Geneva, Switzerland
[l] Center for Mind/Brain Sciences, University of Trento, Rovereto, Italy
[m] Lausanne University Hospital (CHUV) and University of Lausanne (UNIL) Lausanne, Department of Radiology, Lausanne, Switzerland

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ABSTRACT

Resting-state functional connectivity (FC) MRI is sensitive to brain changes in Alzheimer's disease in preclinical stages, however studies in persons with subjective cognitive decline (SCD) have reported conflicting findings, and no study is available at 7T MRI. In this study, we investigated FC alterations in sixty-six participants recruited at the Geneva Memory Center (24 controls, 14 SCD, 28 cognitively impaired [CI]). Participants were classified as SCD if they reported cognitive complaints without objective cognitive deficits, and underwent 7T fMRI to assess FC in canonical brain networks and their association with cognitive/clinical features. SCD showed normal cognition, a trend for higher depressive symptoms, and normal AD biomarkers. Compared to the other two groups, SCD showed higher FC in frontal default mode network (DMN) and insular and superior temporal nodes of ventral attention network (VAN). Higher FC in the DMN and VAN was associated with worse cognition but not depression, suggesting that hyper-connectivity in these networks may be a signature of age-related cognitive decline in SCD at low risk of developing AD.

1. Introduction

Subjective cognitive decline (SCD) is a clinical condition characterized by the subjective perception of a worsening of cognitive function that is not supported by objective neuropsychological assessment (Jessen et al., 2014). Although in most cases this condition is benign and not associated with cognitive decline, it may represent in some cases a preclinical manifestation of Alzheimer's Disease (AD) (Jessen et al., 2014). SCD individuals have a higher risk of developing cognitive decline than persons who do not report cognitive concerns (Mitchell et al., 2014; Lee et al., 2020), and approximately 20 % of SCD individuals develop some form of cognitive deterioration over time (Li et al., 2023). Risk of cognitive decline seems higher in SCD participants recruited from memory clinics than from the community (Slot et al., 2019; Snitz et al., 2018) and in the presence of risk factors for AD, such as higher amyloid levels, apolipoprotein E e4 carriage, and worry for memory rather than other cognitive domains (SCD-plus; Jessen et al., 2014; Li et al., 2023). The etiology of SCD is very heterogeneous and

* Correspondence to: Laboratory of Alzheimer's Neuroimaging and Epidemiology (LANE), IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, via Pilastroni 4, Brescia 25125, Italy.
E-mail address: mpievani@fatebenefratelli.eu (M. Pievani).

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may be also related to non-AD pathologies, such as vascular or frontotemporal dementia (Slot et al., 2019), and other medical conditions (Pedro et al., 2016; Balash et al., 2013). Moreover, affective states such as anxiety and depressive symptoms frequently co-exist with SCD. In particular, affective symptoms in this population have been associated with AD biomarkers and cognitive changes over time (Pavisic et al., 2021; Ahn et al., 2021), and depressive symptoms specifically may underlie and interact with SCD (Hill et al., 2016; Zöllinger et al., 2023).

Resting-state functional magnetic resonance imaging (rs-fMRI) may aid in disentangling this heterogeneity *in-vivo* by identifying brain signatures of SCD and their clinical correlates. Previous rs-fMRI studies in clinical syndromes characterized by cognitive deficits such as AD, behavioral disturbances (e.g., behavioral variant frontotemporal dementia - bvFTD), and affective disease (e.g., anxiety and depression) have shown that these diseases are associated with distinct functional connectivity profiles that closely correlate with clinical symptoms. A large body of literature has shown that AD is characterized by reduced functional connectivity (FC) in the default mode network (DMN) and aberrant FC in networks supporting executive functions and saliency, such as the frontoparietal (FPN) and the ventral attention (VAN) networks (Pievani et al., 2014; Badhwar et al., 2017; Seeley et al., 2009; Pini et al., 2022). The connectivity profile is distinct from that observed in behavioral and affective diseases, bvFTD being primarily associated with reduced FC in VAN (Seeley et al., 2009; Pievani et al., 2014), depression to DMN hyper-connectivity and FPN hypo-connectivity (Kaiser et al., 2015; Zhao et al., 2019), and anxiety with dysregulation of the VAN and reduced connectivity of this circuit with FPN and DMN (Xu et al., 2019; Northoff, 2020). Accordingly, we postulate that rs-fMRI may be sensitive to SCD features and identify a specific connectivity pattern. rs-fMRI has proven capable of recapitulating AD-like patterns in individuals at risk of AD, such as persons with amyloidosis or carriers of susceptibility factors such as the e4 allele of the apolipoprotein E gene (APOE4). Studies in these populations reported reduced FC in the DMN (primarily in hippocampal and posterior cingulate cortex, together with increased FC in frontal regions of the DMN or other networks; Jones et al., 2016; Palmqvist et al., 2017; Jovicich et al., 2019; Hohenfeld et al., 2018). A similar pattern of DMN alterations has been hypothesized in cognitively unimpaired individuals with SCD due to AD, however to date the literature has been conflicting on this issue (Parker et al., 2022). While some studies showed DMN hypo-connectivity in posterior regions (Zajac et al., 2020; Viviano et al., 2019; Viviano and Damoiseaux, 2021; Wang et al., 2013), a majority reported DMN hyper-connectivity in both posterior and frontal areas (Lee et al., 2023; Chiesa et al., 2019; Kawagoe et al., 2019; Dillen et al., 2016; Hafkemeijer et al., 2013), and a few studies reported no difference or mixed results (Zhou et al., 2022; Xu et al., 2019). Moreover, the specificity of the observed FC abnormalities for AD has been questioned by recent studies reporting that FC abnormalities are independent of amyloid (Jiang et al., 2023; Chiesa et al., 2019; Krebs et al., 2023; Chen et al., 2021) and are associated more strongly with worries about cognitive decline rather than actual cognitive deficits (Kawagoe et al., 2019; Jiang et al., 2023; Attaallah et al., 2022).

A better characterization of SCD individuals on the one hand, and more sensitive tools to functional changes on the other hand, seem necessary to disentangle these conflicting results. Conventional 3T MRI systems may be limited in their ability to investigate subtle FC changes due to their relatively low spatial resolution, a limitation especially relevant for small regions such as the hippocampus, which is involved in AD. Compared to 3T MRI systems, 7T MRI offers a higher signal-to-noise (SNR) ratio and enhanced BOLD contrast, which can be traded for higher spatial resolution (De Martino et al., 2011), providing greater sensitivity to BOLD signal in both cortical layers and subcortical regions. To date, 7T MRI has been primarily utilized to assess brain atrophy and vascular pathology in the context of AD (Düzel et al., 2021). However, to our knowledge, no study has used ultra-high magnetic fields to investigate FC in this population. Based on this background, in this study we used 7T fMRI to (i) test the feasibility of identifying FC network alterations in SCD, and (ii) investigate the clinical relevance of FC alterations by assessing their associations with cognitive and affective features.

2. Methods

2.1. Population

Participants were recruited at the Memory Clinic of Geneva University Hospitals (GMC) in the context of the COSCODE project (Ribaldi et al., 2021). In the current study, we included the subgroup of COSCODE participants undergoing 7T MRI, among healthy controls (HC), SCD, and individuals with cognitive impairment (CI). COSCODE clinical workup consists of three visits: (i) cognitive screening using the MMSE, Three-Objects-Three-Places Test, and Clock Drawing Test, (ii) comprehensive cognitive assessment, and (iii) deep cognitive phenotyping (Ribaldi et al., 2021). Additionally, all cases are discussed in a memory board by a group of clinicians and neuropsychologists. Participants were considered to have SCD if they consulted to the GMC for self-experience of deterioration in cognitive abilities but scored within the normal range on all cognitive tests. HC were recruited among volunteers who showed normal cognition and presented no complaints about their cognitive status, and CI were patients with a diagnosis of mild cognitive impairment or dementia based on the respective clinical diagnostic criteria (Albert et al., 2011; McKhann et al., 2011). The study was conducted in concordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. All the procedures were approved by the local ethics committee (PB_2016–01346 and 2020_00403) and participants provided written informed consent prior to enrollment in the study.

2.2. Clinical and cognitive assessment

The neuropsychological assessment included tests assessing global cognition (MMSE), episodic memory (Free and Cued Selective Reminding Tests [FCSRT] immediate and delayed recall tests, digit span forward test), attention/executive functions (Trail Making Test [TMT] part A and B, digit span backward test, digit symbol test), language (category and phonemic fluency tests), visuospatial functions (constructional praxis copy CERAD subtest). For ease of interpretation, each cognitive score was adjusted for age, gender, and education and converted to a W-score using the HC group as reference. To reduce the number of variables, composite scores were derived for three cognitive domains (i.e., memory, attention/executive functions, and language) by averaging the W-scores of tests within the specific cognitive domain. For attention/executive functions, the inverse of TMT-A and TMT-B data was calculated for consistency with other scores.

Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale subscales (HADS-A and HADS-D, respectively). A score above 7 on the HADS-A or HADS-D is indicative of the presence of anxiety or depressive symptoms, while a score above 11 is considered pathological.

2.3. MRI protocol

Images were acquired at the Swiss Federal Institute of Technology in Lausanne (EPFL) on a 7T scanner (MAGNETOM, Siemens Healthineers, Erlangen, Germany) equipped with a single-channel transmit/32-channel receive head coil (Nova Medical). The following sequences were collected: (i) T1-weighted anatomical using 3D Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) sequence ($TI_1/TI_2/TE$ = 800/2700/2 ms, TR = 6000 ms, flip angle = 7°/5°, voxel size = 0.6 × 0.6 × 0.6 mm, 3-fold in-plane acceleration, 256 slices); (ii) high-resolution rs-fMRI with multiband echo planar imaging (EPI) sequence (TE = 26 ms, TR = 1550 ms, flip angle = 63°, voxel size = 1.3 × 1.3 × 1.4 mm, 3-fold in-plane acceleration, 3-fold multiband acceleration, 93

slices, 250 volumes), (iii) short rs-fMRI EPI sequence acquired with reversed phase encoding direction for distortion correction (TE = 26 ms, TR = 1550 ms, flip angle = 63°, voxel size = 1.3 × 1.3 × 1.4 mm, 3-fold in-plane acceleration, 3-fold multiband acceleration, 93 slices, 5 volumes).

2.4. Resting-state fMRI pre-processing

Image processing was performed with Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs/), FSL (http://fsl.fmrib.ox.ac.uk/fsl/), LAYNII (http://github.com/layerfMRI/LAYNII) and MATLAB (The Mathworks, Natick, MA, USA) software. The first 5 volumes of each rs-fMRI scan were discarded to allow for signal stabilization and a brain-mask was created from the first volume of this time-series using FSL *bet* routine and used as region-of-interest for denoising, which was performed using Marchenko-Pastur Principal Component Analysis (Veraart et al., 2016). The denoised rs-fMRI images were corrected for motion with *MCFLIRT* and assessed for motion outliers with *fsl_motion_outliers* (both part of FSL). Excessive motion, defined as head movements > 2 mm/degrees or a framewise displacement > 0.5 mm, led to the exclusion of four CI participants. Susceptibility induced distortions correction was carried out with ANTs as follows: EPI time-series acquired with reversed phase encoding direction (AP and PA) were averaged with *antsMotionCorr*, bias field corrected with *N4BiasFieldCorrection* (Tustison et al., 2010), and unwarped using the *antsMultivariateTemplateConstruction* routine in ANTs with Greedy-SyN transformation model and cross-correlation similarity metric (Avants et al., 2008). This step generates a template EPI image that is corrected for distortions, together with the corresponding unwarping transformations (affine and non-linear). The motion corrected EPI time-series were rigidly aligned to the EPI template using *antsRegistration* (part of ANTs) and corrected for distortions using the unwarping transformations. Two SCD participants were excluded from subsequent analyses due to lacking images with reversed phase encoding direction for distortion correction. Distortion corrected EPI time-series were bias field corrected with *N4BiasFieldCorrection* and smoothed using the anatomically informed L*N_GRADSMOOTH* module of LAYNII package (Huber et al., 2021). Spatial smoothing was kept to a minimum using a 2 mm full width at half maximum (FWHM) kernel and a selectivity value of 0.5. Independent component analysis-based automatic removal of motion artefacts tool (ICA-AROMA, part of FSL; Pruim et al., 2015) was used to identify and remove residual motion-related rs-fMRI components using non-aggressive denoising. Nuisance regression was carried out on ICA-AROMA output by regressing out non-neuronal signals (i.e., white matter [WM] and cerebrospinal fluid [CSF]) with the *fsl_regfilt* command of FSL. WM and CSF compartments were segmented from the bias-field (via *N4BiasFieldCorrection* routine) and skull-stripped (via *antsBrainExtraction* routine) MP2RAGE scans using FSL's *fast* tool and a three-class segmentation. The CSF and WM compartments were thresholded at 0.95, binarized, and registered to the EPI scan using the inverse of a boundary-based registration co-registering EPI to MP2RAGE scan (*epi_reg*, part of FSL). Finally, the nuisance corrected rs-fMRI time-series were detrended with high-pass filtering at 0.01 Hz with FSL. The resulting fMRI time-series were registered to the standard Montreal Neurological Institute (MNI) space using a combination of rigid, linear and non-linear transformations with ANTs. First, unsmoothed EPI scans were rigidly aligned to the corresponding MP2RAGE images using *antsRegistration* and Mattes Mutual Information metric. Subsequently, the MP2RAGE scans were non-linearly registered to a custom anatomical template using *antsRegistrationSyN* routine with a combination of rigid, affine, and non-linear transformations (Mattes Mutual Information metric was used for the rigid and affine steps, cross-correlation similarity metric for the non-linear step). The custom template was created from the MP2RAGE images of 16 individuals (8 younger adults and 8 older adults scanned on the same 7T machine, age range: 18–83 years) using *antsMultivariateTemplateConstruction* routine with Greedy-SyN transformation model and cross-correlation similarity metric. Finally, the custom template was registered to the MNI template with *antsRegistration* using a combination of rigid, affine, and non-linear transformations. All the above transformations were concatenated and applied with *antsApplyTransforms* to the detrended and band-pass filtered rs-fMRI time-series. EPI scans were resampled to a voxel size of 1.5 mm isotopic to preserve the original resolution.

2.5. Independent component analysis (ICA)

Melodic ICA (Beckmann and Smith, 2004) and dual regression (Beckmann et al., 2009) toolboxes were used to extract large-scale functional networks. Group-level melodic ICA was carried out on the whole sample (i.e., HC, SCD, CI) to decompose the rs-fMRI data into spatially independent components and time-courses. The number of components was set to n = 70, corresponding to a higher-order decomposition as in previous studies (Smith et al., 2009; Abou-Elseoud et al., 2010). The set of spatial components from the group-level analysis was used to generate subject-specific versions of the spatial maps and associated timeseries using *dual_regression* FSL routine. First, for each participant, the group-average set of spatial maps was regressed (as spatial regressors in a multiple regression) into the participant's 4D space-time dataset, thus resulting in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries were regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

We selected canonical resting-state networks involved in AD and affective diseases (DMN, DAN, VAN and FPN), and control networks such as the sensorimotor (SMN) and visual (VIS) networks. Networks were identified based on a template matching procedure using two parcellations (Shirer et al., 2012; Schaefer et al., 2018) and visual inspection. To ensure reliability of the template matching procedure, only the components consistently identified with both parcellations were included in the statistical analyses.

2.6. Biomarkers assessment

Biomarkers of amyloid, tau, and neurodegeneration (ATN) were collected for a subgroup of participants as part of their diagnostic workup or other research projects. Amyloid was assessed with amyloid-PET images acquired using 18F-florbetapir (50 min after injection of 200 MBq, 3 5-min frames) or 18F-flutemetamol (90 min after injection of 150 MBq, 4 5-minutes image frames) tracers. Tau was assessed on tau PET images acquired using 18F-flortaucipir (75 min after injection of 180 MBq, 6 5-min frames). Neurodegeneration markers were assessed on T1-weighted images acquired on clinical 3T scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). Both dichotomous and continuous measures of amyloid and tau pathology were assessed. For dichotomous measures, amyloid and tau PET scans were classified as positive or negative by a board-certified specialist in nuclear medicine (VG) using visual assessment and published guidelines. European Medicines Agency guidelines were used to determine amyloid PET positivity (https://www.ema.europa.eu/en/medicines/human/EPAR/amyvid, https://www.ema.europa.eu/en/medicines/human/EPAR/vizamyl). Tau positivity was determined based on Braak neuropathological staging (Braak et al., 2006) and defined as Braak stages IV-VI (Fleisher et al., 2020; Mathoux et al., 2024). To derive continuous measures of pathology, amyloid and tau PET scans were processed using an in-house standard pipeline as described previously (Boccalini et al., 2024). Standardized uptake value ratios (SUVr) were extracted and normalized to the cerebellum as reference region for amyloid PET and cerebellar crus for tau PET. Amyloid SUVr was converted into Centiloid scale according to the Global Alzheimer's Association Interactive Network guidelines (Klunk et al., 2015). Bilateral hippocampal volumes were extracted as markers of neurodegeneration using FreeSurfer

version 7.0 (recon-all - https://surfer.nmr.mgh.harvard.edu/), averaged, and normalized by total intracranial volume. APOE genotype was determined according to combination of both SNP rs429358 and rs429358 (Corder et al., 1993; Saunders et al., 1993) using a TAQMAN base assay on a Real-Time PCR instrument (LightCycler 480, ROCHE, Vienna, Austria) using commercial reagents (TaqMan SNP genotyping assays, ThermoFisher Scientific, Waltham, MA, USA), on DNA extracted from venous blood from participants. DNA were extracted using an automated protocol (QiaSymphony, Qiagen, Hilden, Germany).

2.7. Statistical Analysis

Demographic, clinical, and biomarker variables. Differences between groups in demographic, cognitive, and ATN biomarker features were assessed with Analysis of Variance (ANOVA) for continuous variables and Chi-squared test for categorical variables. Bonferroni test was used for post-hoc comparisons between groups. A p-value of 0.05 was considered as the significance level for all statistical comparisons.

FC measures. Voxel-level differences in FC between the three groups were assessed with FSL's general linear model using F- and t-tests. For each network, we first performed an F-test across the three groups to identify significant intergroup differences. When an F-test was significant, we carried out post-hoc two-sample t-tests to identify pairwise differences between groups (i.e., SCD vs. HC, SCD vs. CI, CI vs. HC). FC maps were corrected for multiple comparisons across space using family-wise error (FWE) correction and non-parametric permutation testing at a threshold-free cluster enhancement (TFCE) level of $p < 0.05$ (FSL's *randomise* tool; Winkler et al., 2014; n = 5000 permutations, minimum cluster size of 10 voxels). Age and gender were entered as covariates of no interest in all the models. Each contrast was restricted to the corresponding network spatial map that was extracted using a one sample t-test (corrected for multiple comparisons at the cluster level using FWE correction at $p < 0.001$ with *randomise*) and binarized. Low SNR regions (i.e., orbitofrontal and olfactory cortices, cerebellum, and pallidum) were also excluded from the analysis (see Suppl. Fig. 1 and Suppl. Table).

Correlations between connectivity, cognitive, and biomarker features. Correlations between variables were tested with linear regression models using the *lm* function. All models were tested for heteroscedasticity with the Breusch-Pagan Test (*bptest*) and when heteroscedasticity was present the response variables were log-transformed to increase the normality of data. Two sets of correlations were conducted, as follows. First, to evaluate the clinical relevance of FC alterations in SCD, we assessed correlations between significant network features and cognitive/clinical measures in the SCD group only. For each significant F-contrast, the mean connectivity was computed from (i) the whole network (i.e., the spatial map derived from one sample t-test), and (ii) the significant clusters resulting from the two-sample t-tests. For the latter, we combined the local clusters from each t-contrast into a single region to derive a unique connectivity measure. Cognitive/clinical features were global cognition (MMSE), specific cognitive domains (three composite scores and visuospatial abilities), anxiety and depression as assessed by the HADS scale (n = 7 measures). The significance level was set to $p < 0.05$ uncorrected for multiple comparisons. In addition, we reported the results after multiple comparisons correction with Bonferroni correction. Second, correlations between ATN markers and (i) FC and (ii) cognition were carried out in the whole sample for descriptive purposes, since AD biomarkers were available only for a subsample of participants. For this analysis, continuous ATN measures (amyloid Centiloid, tau global SUVR, bilateral hippocampal volume), previous FC measures, and cognitive measures (MMSE and four cognitive domains) were included and adjusted for age and gender to account for differences between groups. Significance level was set to $p < 0.05$ uncorrected for multiple comparisons.

3. Results

3.1. Demographic, cognitive, and biomarker features

The clinical and biomarker characteristics of HC (n = 24), SCD (n = 14) and patients with CI (n = 28) are reported in Table 1. The majority of CI patients had a clinical diagnosis of MCI (26 out of 28, 93 %) and were more frequently amyloid positive (12 out of 21, 57 %). Amyloid negative CI patients were all classified as MCI, and their etiological diagnoses were AD (n = 1), suspected frontotemporal lobar degeneration (1), vascular (1), or undetermined (n = 6). There were no differences between groups in education, HADS-A subscale, and number of comorbidities (all $p > 0.05$), while significant differences were observed in HADS-D subscale (SCD having a greater proportion of depressive symptoms than HC; $p = 0.031$). Cognitive assessment showed no differences between SCD and HC in global cognition or specific cognitive

Table 1
Sociodemographic, clinical, cognitive, and biomarker features of the study groups.

	Healthy Controls	Subjective Cognitive Decline	Cognitively Impaired	*P*
N	24	14	28	
Demographic				
Age, years	62.7 ± 7.8	66.9 ± 13.2	69.7 ± 7.8*	**< 0.001**
Gender, female (%)	18 (75 %)	9 (64 %)	8 (29 %)*	**0.002**
Education, years	15.5 ± 3.0	16.5 ± 3.5	14.5 ± 4.1	0.185
Clinical				
HADS-A>7, N (%)	5 (21 %)	5 (36 %)	8 (29 %)	0.598
HADS-A	5.2 ± 3.9	6.3 ± 2.7	6.5 ± 3.9	0.175
HADS-D>7, N (%)°	0 (0 %)	4 (29 %)$	4 (15 %)	**0.031**
HADS-D	2.4 ± 1.7	4.5 ± 3.4	4.1 ± 3.6	**0.044**
N of somatic diseases°	1.8 ± 1.6	3.0 ± 1.9	2.6 ± 1.6	0.263
Cognitive (W-scores)				
MMSE°	0.00 ± 1.00	0.50 ± 1.25	−2.25 ± 4.41*#	**0.009**
Memory	0.00 ± 0.62	−0.63 ± 0.64	−1.56 ± 1.57*	**< 0.001**
Attention/ executive^	0.01 ± 0.77	−0.44 ± 0.51	−0.81 ± 1.03*	**0.001**
Language&	0.00 ± 0.89	−0.55 ± 1.02	−0.97 ± 0.87*	**< 0.001**
Visuospatial£	0.00 ± 1.00	−0.53 ± 1.82	−0.95 ± 1.90	0.058
AD biomarkers				
Amyloid positive, N (%)	2/19 (11 %)	2/10 (20 %)	12/21 (57 %)*	**0.005**
Tau positive, N (%)	0/10 (0 %)	0/7 (0 %)	6/22 (27 %)	0.064
Hippocampal volume (mm^3)[a]	3930 ± 438	3745 ± 455	3493 ± 543*	**0.007**
APOE e4 carriers, N (%)	3/24 (13 %)	1/13 (8 %)	7/27 (26 %)	0.267

Data represent mean ± standard deviation or frequency (percentage). P denotes significance on Analysis of Variance (ANOVA) test (continuous variables) or Chi-square test (categorical variables). Post-hoc comparisons for continuous variables were tested using Bonferroni test.
* different between cognitively impaired (CI) and healthy controls (HC).
# different between CI and subjective cognitive decline (SCD).
$ different between SCD and HC.
° data missing for 1 CI. ^ data missing for 2 SCD and 2 CI. & data missing for 2 SCD and 8 CI. £ data missing for 2 HC, 3 SCD and 10 CI.
[a] MRI data missing for n = 6 HC and 7 CI.
Abbreviations: AD: Alzheimer's disease; APOE: apolipoprotein E; HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale - depression subscale; MMSE: Mini-Mental State Examination.

domains (all $p > 0.05$; Table 1). The proportion of SCD participants with abnormal AD biomarkers was low: only one participant was an APOE4 carrier (data available for n = 13 SCD), two showed amyloid positivity on visual rating (data available for n = 10 SCD; one APOE4 carrier and one non-carrier), none showed tau positivity on visual rating (data available for n = 7 SCD), and hippocampal volumes were comparable to HC (Table 1).

Compared to HC, CI participants were older ($p = 0.021$) and included more men ($p = 0.002$), while no difference was detected with SCD in these measures ($p > 0.05$). CI patients performed worse than HC in all cognitive domains ($p < 0.05$), and worse than SCD in global cognition (MMSE; $p = 0.020$) and memory ($p = 0.004$; Table 1). Compared to HC, CI participants were more frequently amyloid positive (57 % vs 11 %; $p = 0.006$) and showed lower hippocampal volumes ($p = 0.022$).

3.2. Networks FC analysis

Group-level melodic ICA identified 3 components corresponding to the DMN (Suppl. Fig. 2): a component anchored to the posterior cingulate cortex (DMN1), the classical DMN component including both medial and lateral hubs in frontal, temporal and parietal regions (DMN2), and a frontal component including the anterior cingulate and dorsal frontal cortex (DMN3). ICA decomposition identified a single component corresponding to the DAN, VAN, and SMN, and two components corresponding to the FPN (left and right hemispheres, respectively) and the VIS network (medial and lateral parcellations, respectively).

The voxel-wise analysis showed significant between-group differences of intrinsic connectivity (z-scores) on F-test for the following network components (Fig. 1; Table 2): DMN2 ($p = 0.03$, FWE-corrected at cluster-level) and VAN ($p = 0.01$, FWE-corrected at cluster-level). Post-hoc pairwise 2-sample t-tests showed that in DMN2, SCD had higher functional connectivity than HC in the left middle frontal cortex (cluster 1: Cohen's $d = 1.11$; Fig. 1, **top left**) and higher connectivity than CI patients in the left superior and middle frontal cortex (cluster 2: Cohen's $d = 1.78$; Fig. 1, **bottom left**). For the VAN, SCD showed higher FC than HC in the right temporal superior cortex, right insula, right temporal superior pole, and left insula (cluster 3: Cohen's $d = 1.41$; Fig. 1, **top right**), and higher FC than CI patients in the right temporal superior and middle cortex, right supramarginal gyrus, right postcentral gyrus, and right rolandic operculum (cluster 4: Cohen's $d = 2.05$; Fig. 1, **bottom right**). No difference was detected between groups in the FPN and DAN networks, nor in control networks (SMN and VIS networks; all $p > 0.05$ FWE-corrected at cluster-level).

3.3. Correlations between FC, cognitive and clinical features in SCD

In the SCD group, higher FC in the whole DMN was associated with lower memory scores ($t = -2.351$, $p = 0.041$; Fig. 2). Higher FC in cluster 1 (left middle frontal DMN) was associated with lower MMSE scores ($t = -3.259$, $p = 0.007$; Fig. 2), and higher FC in VAN cluster 4 was associated with lower visuospatial scores ($t = -2.63$, $p = 0.027$; Fig. 2). These correlations were not significant after correction for multiple comparisons ($p < 0.0012$). No association was detected between FC and depression/anxiety subscales (all $p > 0.05$), both at the uncorrected and corrected level.

3.4. Correlations between ATN markers, FC and cognition in the whole sample

In the whole sample, higher amyloid uptake showed a trend for an association with lower FC in the VAN (cluster 4: $t = -2.009$, $p = 0.051$; Suppl. Fig. 3; model adjusted for age and gender), while no association was detected between T/N markers (i.e., tau uptake and hippocampal volumes) and FC ($p > 0.05$). In the whole group, higher tau uptake correlated with lower memory scores ($t = -2.066$, $p = 0.048$) and smaller hippocampal volumes correlated with lower memory ($t = 3.635$, $p < 0.001$; Suppl. Fig. 3; models adjusted for age and gender). No association was detected between amyloid uptake and cognitive tests ($p > 0.05$).

4. Discussion

This study is the first to examine FC alterations at 7T MRI in participants with SCD recruited from a memory clinic, and to explore their association with cognitive and clinical features. We found higher FC in the DMN and VAN in SCD participants compared to HC and CI patients, particularly in the frontal regions of the DMN and the frontal-temporal areas of the VAN. This heightened FC was linked to poorer cognitive performance, though it was not associated with anxiety or depressive symptoms. Notably, FC abnormalities were observed in SCD participants whose cognitive and biomarker profiles did not suggest preclinical AD, indicating that functional hyper-connectivity might represent a marker

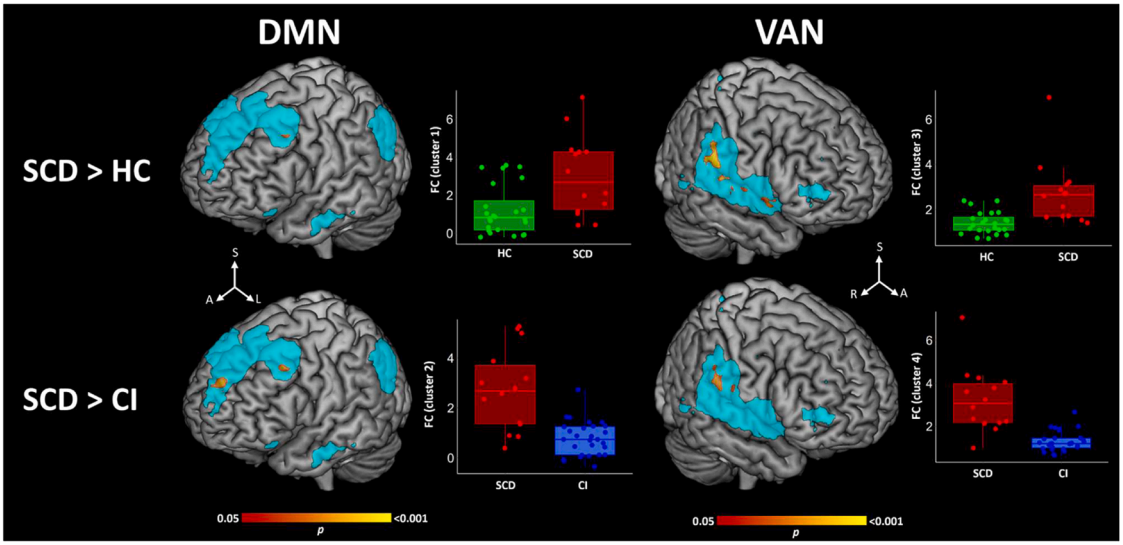

Fig. 1. Results of the voxel-wise analysis: functional connectivity differences (red-yellow coloured clusters) between SCD, CI and HC ($p < 0.05$, FWE-corrected at the cluster-level, minimum cluster size >10 voxels) overlaid on group networks (light blue). CI: cognitively impaired, DMN: default mode network, HC: healthy controls, SCD: subjective cognitive decline, VAN: ventral attention network.

Table 2
Voxel-wise comparisons of intrinsic functional connectivity between groups with subjective cognitive decline (SCD), healthy controls (HC), and cognitively impaired (CI). Differences were assessed with FSL's general linear model (F-test followed by post-hoc t-tests) including age and gender as covariates. F and t-tests were corrected for multiple comparisons at the cluster-level using family-wise error (FWE) correction at $p < 0.05$ and a minimum cluster size of 10 voxels.

Network	Contrast	Cluster	T	MNI			N of voxels
		(local maxima)		X	Y	Z	
DMN2	**SCD>HC**	**1**					
		Frontal middle L	4.61	−43.5	18	43.5	38
DMN2	**SCD>CI**	**2**					
		Frontal superior L	4.98	−12	58.5	30	100
		Frontal middle L	5.01	−42	21	43.5	60
VAN	**SCD>HC**	**3**					
		Temporal superior R	5.37	51	−18	10.5	599
		Temporal superior/Insula R	5.57	40.5	−19.5	0	160
		Insula R	4.97	40.5	1.5	6	148
		Temporal pole superior R	4.36	55.5	12	−3	75
		Insula/putamen L	4.77	−34.5	−6	−1.5	24
		Temporal superior R	3.91	66	−13.5	6	21
		Temporal superior R	4.01	58.5	−6	4.5	11
VAN	**SCD>CI**	**4**					
		Temporal middle R	5.04	37.5	−52.5	19.5	108
		Supramarginal R	4.2	63	−31.5	25.5	104
		Temporal superior R	4.8	51	−18	10.5	86
		Postcentral R	4.14	66	−10.5	36	59
		Rolandic operculum R	3.91	49.5	−27	22.5	30
		Temporal superior R	4.97	40.5	−19.5	0	18

Results are reported at a p value < 0.05 corrected for family-wise error rate (FWE).
Abbreviations: DMN2, default mode network (component 2); L, left; MNI, Montreal Neurological Institute; R, right; VAN, ventral attention network.

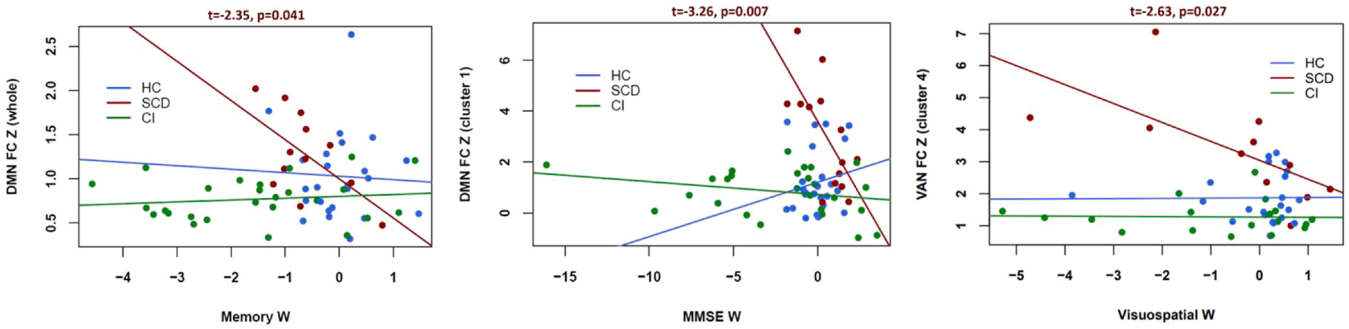

Fig. 2. Correlations between functional connectivity and cognition (expressed as W-scores) in SCD participants. CI: cognitively impaired, DMN: default mode network, FC: functional connectivity, HC: healthy controls, MMSE: Mini-mental state examination, SCD: subjective cognitive decline, VAN: ventral attention network.

of early cognitive decline in individuals at low risk for AD. Unlike previous fMRI studies that connected FC alterations in SCD to AD pathology or affective states, our findings propose an alternative explanation: the presence of a SCD subgroup with a potentially more benign trajectory, such as age-related cognitive decline or "worried well" individuals. This interpretation is supported by the specific topography of the FC differences, the observed cognitive-imaging correlations, and the biomarkers profile of the participants.

Our finding of DMN hyper-connectivity in SCD compared to HC and CI is in line with several previous studies carried out on standard (i.e., 3T) scanners (Chiesa et al., 2019; Hafkemeijer et al., 2013; Dillen et al., 2016; Kawagoe et al., 2019) showing that DMN alterations are a signature of SCD. However, in contrast to previous reports, the topography of DMN FC alterations in the present study was not suggestive of an AD pattern, as we detected differences in the anterior frontal cortex, while previous studies also reported alterations in temporal and parietal hubs of the DMN such as the hippocampus and posterior cingulate cortex (Lee et al., 2023; Hafkemeijer et al., 2013; Chiesa et al., 2019; Dillen et al., 2016). Another difference with previous studies is that the other network showing alterations in SCD was the VAN, a circuit that is not clearly affected in AD (Hohenfeld et al., 2018). The VAN is a right-lateralized circuit primarily involved in the detection of relevant stimuli, regulation of behavior and stimulus-driven attention, and switching between DMN and FPN (Seeley et al., 2007; Corbetta and Shulman, 2002). Key nodes of the VAN are the insula, anterior cingulate cortex, superior temporal gyrus and the temporo-parietal junction, and dysfunction of this circuit has been implicated in diseases characterized by behavioral and affective disturbances such as frontotemporal dementia and anxiety disorders (Menon, 2011). In our study, SCD showed higher connectivity in insular and superior temporal cortex areas of the VAN, thus our FC pattern may denote a signature of increased worries and/or affective symptoms in SCD. This interpretation is supported by recent studies showing that VAN and DMN hyper-connectivity in SCD is associated with negative emotions (Schwarz et al., 2022), higher degree of worries (Jiang et al., 2023), and faster response to uncertainty (Attaallah et al., 2022). However, this explanation is not supported by our data since we observed only a trend for higher depressive symptoms in SCD and no association between depressive symptoms and FC in this group.

Studies in SCD are frequently discussed in the framework of AD given that SCD was conceptualized in this context (Jessen et al., 2014). Accordingly, AD-related mechanisms such as amyloid pathology and neurodegeneration have been proposed to explain functional alterations in SCD. In our cohort, FC changes followed a non-linear trajectory, whereby FC was higher in SCD compared to HC and lower in CI patients compared to SCD, congruently with previous studies in AD clinical

spectrum (Viviano and Damoiseaux, 2020). It has been hypothesized that hyper-synchrony in SCD might denote a compensation for early AD pathology, based on preclinical evidence that amyloid accumulation and APOE4 status are associated with brain hyper-synchrony (Palop and Mucke, 2016; Giorgio et al., 2024), however this hypothesis is unlikely to explain our results since our SCD participants showed little evidence of AD pathology, as only 2 participants had biomarkers suggestive of AD such as amyloid positivity or APOE4 carriage. Moreover, while our sample size did not enable to test associations between FC and ATN markers in the SCD group, correlations in the whole cohort showed a trend for a negative association with VAN FC and no association with the DMN. Overall, these observations are in line with recent studies indicating that hyper-connectivity in SCD may be unrelated to AD pathology (Jiang et al., 2023; Chiesa et al., 2019). The hypothesis that FC alterations may reflect neurodegenerative processes is also not supported by our data, since SCD showed no evidence of neurodegeneration (as assessed with hippocampal atrophy). Conversely, the decline in DMN and VAN FC in CI patients is consistent with their clinical-biomarker profile and suggests a neurodegenerative etiology, the majority of CI patients being amyloid positive and showing greater hippocampal atrophy than HC.

The cognitive profile of our SCD cohort was within the normal range, in line with the definition of SCD and with the view that SCD may not reflect incipient cognitive decline (Kawagoe et al., 2019). Still, we cannot exclude the possibility of subthreshold age-related cognitive impairment as our functional-cognitive correlations showed that DMN hyper-connectivity was associated at trend level with lower scores in memory and global cognition, while VAN hyper-connectivity was associated with lower visuospatial functions. In models of physiological aging, higher FC coupled with worse cognitive performance might reflect less efficient network processing or compensatory mechanisms in response to aging associated cognitive decline (Morcom and Henson, 2018). Our data are more congruent with this model than alternative explanations linking lower cognitive performance in SCD to excessive worries or affective states, as we did not observe an association between higher FC and affective measures in our sample. Longitudinal and larger dataset are needed to determine whether the cognitive performance of SCD participants will decline over time, and whether it is influenced by affective factors such as depression and anxiety.

Our observation of a low prevalence of APOE4 carriage, amyloid and tau pathology and neurodegeneration in SCD identifies a potentially distinct sub-group with a low risk of developing AD. This observation highlights the importance of assessing the presence (or lack thereof) of AD pathology when investigating SCD and the need to better characterize this population at the clinical and biomarker level. With the increasing number of individuals referring to memory clinics with SCD and the recent approval of disease-modifying drugs for AD by the FDA (Rabinovici and La Joie, 2023), distinguishing SCD at risk of AD from those due to non-AD causes is increasingly critical for adequate referral and management by specialists and planning of interventions (Frisoni et al., 2023). Indeed, while individuals with SCD due to AD pathology may benefit from secondary prevention interventions for AD, SCD due to affective disorders may benefit the most from interventions targeting psychosocial or affective factors, and participants with age-related cognitive decline from risk reduction programs (e.g., brain health services).

Another novelty of this study is the demonstration of the feasibility of investigating a population at risk of dementia using a 7T fMRI system. 7T MRI has long been used almost exclusively in research settings, but this may rapidly change with the recent approval of 7T devices for clinical use (Cosottini and Roccatagliata, 2021). Notwithstanding known issues of discomfort related to the higher field strength, all HC and SCD participants were able to successfully complete the 7T scan, and the only participants excluded due to excessive motion or incomplete scans were CI patients, in line with the observation that impaired patients tend to move to a greater extent. The results are thus encouraging for future studies aimed at exploring early functional changes in populations at risk of AD.

Finally, we acknowledge some limitations of our study. The sample size was small, especially for the SCD group, and the cross-sectional design did not allow to ascertain whether participants with SCD progressed to dementia over time, thus longitudinal and larger studies are needed to confirm our preliminary results. Notably, in our study we did not detect FC differences in patients with CI that have been reported previously at 3T (Pievani et al., 2014; Badhwar et al., 2017). Possible factors that may have contributed to this null effect are the characteristics of our sample, such as clinical and biological heterogeneity of CI patients, and the small sample. Also, differences in demographic features between groups might have influenced the results. However, since we accounted for age and gender in the models and there were no differences between SCD and HC in these variables, it is unlikely that this issue affected to a large extent results in SCD. Moreover, ATN biomarkers were available only in a subgroup of participants, which limited our power to investigate associations between imaging and biological markers in the SCD subgroup and to carry out analyses stratified for biomarker status. In the future, the availability of blood-based biomarkers will facilitate the characterization of larger SCD cohorts. Finally, we acknowledge that our study was not designed to evaluate specific advantages of 7T relative to 3T. To better understand the extent to which our findings were affected by the high-field scanner factor, a study with the same population at 7T and 3T would be more appropriate, which is beyond the scope of our study. From a technical point of view, 7T MRI may be more susceptible than 3T systems to artifacts due to physiological fluctuations, signal drops, or motion, which can affect BOLD signal measurements especially in CI patients. In the current study, we tried to minimize these issues by implementing pre-processing steps to account for and reduce the impact of artifacts and motion (ICA-AROMA), including ad-hoc tools developed for the analysis of 7T MRI data (anatomically informed smoothing), and we accounted for signal drops by removing voxels with lower tSNR from the analysis.

5. Conclusions

These preliminary results support the feasibility of cognitive networks imaging at 7T in populations at risk of dementia from a memory clinic. Our findings show that DMN and VAN hyper-connectivity is present in SCD participants with a low risk of developing AD and is associated with worse cognition. These persons might benefit from risk reduction programs rather than interventions targeting AD pathology or affective factors. Future studies in larger cohorts should investigate the potential of 7T fMRI in classifying distinct clinical/biological SCD subtypes.

Ethics approval statement

All the procedures were approved by the local ethics committee (PB_2016–01346 and 2020_00403). Participants provided written informed consent prior to enrollment in the study.

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Disclosure Statement

The authors declare no conflict of interest in relation to the submitted work.

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Verification

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.09.007.

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