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Original Research Article

Alterations in functional connectivity in individuals with subjective cognitive decline and hippocampal atrophy

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ABSTRACT

Objectives: The aim of this study was to determine whether individuals with Subjective Cognitive Decline (SCD), particularly those with a neurostructural marker of risk for AD (SCD+), exhibit differences in the functional connectivity of the Default-Mode Network (DMN) relative to controls, as this network is known to be altered in the AD continuum.
Design: Cross-sectional study.
Setting: Galicia, Northwest Spain.
Participants: The sample compromised 133 participants: 69 controls, 51 SCD and 13 SCD+.
Measurements: Seed-to-voxel analysis was conducted using four DMN ROIs. Dynamic independent component analysis of the DMN was also performed.
Results: The SCD and SCD+ groups exhibited DMN hyperconnectivity, which was more extensive in the SCD+ group. Increased anti-correlations between DMN and task-positive parietal regions were related to poorer executive scores in SCD+ and a tendency for higher DMN recurrence in SCD+.
Conclusions: Hippocampal atrophy as a SCD+ biomarker is associated with extensive DMN hyperconnectivity and increased anti-correlations between DMN and task-positive network regions.

Introduction

In efforts to provide better and earlier diagnosis of Alzheimer's disease (AD), many studies have focused on identifying neurofunctional indices related to the continuum of the disease [21], including clinical, prodromal and preclinical stages. Subjective cognitive decline (SCD) has been defined as a preclinical entity in which cognitively unimpaired individuals exhibit subjective concerns about a decline in their cognitive abilities [22]. However, ongoing research aims to identify markers that can more accurately link SCD to the AD continuum (SCD+) in order to enable early intervention [22].

Neuroimaging techniques are emerging as valuable tools in the search for objective indices of SCD+ [46]. Analysis of resting-state functional connectivity by using MRI (rs-fMRI) has garnered interest in this field due to the non-invasive nature and ease of use of the technique as well as its wide availability in clinical and research settings. Use of MRI has revealed alterations in the functional connectivity of the default-mode network (DMN) in dementia and prodromal stages [50]. The DMN comprises a group of brain regions including the medial prefrontal cortex, posterior cingulate cortex, angular gyrus and precuneus. In healthy people, the DMN shows robust functional connectivity during resting and deactivation during execution of cognitive tasks [4] The DMN is involved in self-reflection and memory processes, and it is therefore considered particularly vulnerable in AD [7].

Most studies involving SCD (or related entities such as subjective memory complaints) [14,18,25,31,43,7] have observed increased DMN functional connectivity in participants with SCD relative to cognitively unimpaired (CU) participants [14,18,25,31,43,7], while others have

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either observed the opposite [16,47,48] or have not observed any relationship between cognitive complaints and DMN connectivity [10,45].

One possible explanation for these discrepancies is the method used to diagnose SCD. Thus, while some studies have relied on diagnosis based on questions about cognitive performance [43,45], subjective complaint questionnaires [10,14,18,25,7] or reports from informants such as family members [16,47,48], very few have distinguished between participants with risk factors for AD (SCD+) and those without such risk factors (SCD-), despite the SCD initiative recommendations [22].

In this context, some studies have used the presence of the APOE4 allele to distinguish between SCD+ and SCD–. However, again contradictory results have been reported, including a smaller increase in DMN connectivity in participants with SCD possessing the APOE4 allele (SCD+) than in participants with SCD lacking the allele [9], higher functional connectivity in the posterior cingulate cortex of SCD+ participants [13] and no modulation of DMN functional connectivity related to the presence of the APOE4 allele [25]. The heterogeneity of the sample concerning this genetic vulnerability, where participants may be at different stages of neurostructural decline, could also contribute to the lack of consistency across studies, making APOE4 less useful as a biomarker for SCD with risk of AD.

As a biomarker, beta-amyloid deposits are more closely associated with neurostructural integrity in AD. Notably, greater DMN functional connectivity has been observed in SCD+ than in SCD– groups, classified according to beta amyloid levels using the PET technique [27]. However, the aforementioned study did not include a control group. Furthermore, non-invasive methods are required in clinical settings to determine AD risk in individuals without cognitive impairment.

The hippocampus is one of the first structures impacted in the AD continuum [5], and hippocampal atrophy is recognized as a risk factor for progression to AD [36]. Accordingly, the present study used a measure of hippocampal structural integrity to identify study participants with SCD+ following previous suggestions [11,46].

The objective of the present study was to characterize the pattern of DMN functional connectivity in participants with SCD at risk of developing AD, evaluating the differences between SCD+, SCD- and CU groups. Based on the majority of the aforementioned studies, we expect to find differences between SCD participants and the control group (increases in DMN functional connectivity), and to be more pronounced in those participants with hippocampal atrophy (SCD+).

Methods

Participants

The sample comprised 133 participants, who we classified into three groups: cognitively unimpaired (CU), n = 69, subjective cognitive decline without risk of AD (SCD-), n = 51, and SCD with risk of AD (SCD+), n = 13 (see Table 1 for sample characterization). Considering the presence of cognitive complaints in normative aging [35], we took into account the severity of concern [22] and only classified participants as SCD when the complaints exceeded the score in the Questionnaire d'auto-évaluation de la Mémoire (QAM) [3] corresponding to the 5th percentile according to age norms [32]. Individuals with SCD were categorized following the two main criteria proposed by the SCD Initiative Working Group [22]: 1) self-reported persistent decline in cognitive capacity, especially in memory, relative to a previously normal cognitive status, which is unrelated to an acute event; and 2) normal cognitive performance in standardized tests adjusted for age and education. Participants were asked about any self-perceived persistent decline in cognitive capacity and to express their worries about their failures in attention and memory in the last few years. Possible known explanations for these complaints were ruled out in the initial interview (e.g. psychiatric disorders).

To identify those participants at risk of AD (SCD+), the hippocampal volume of each participant was determined. A sagittal T1-weighted 3D-MPRAGE sequence was preprocessed with the FreeSurfer 6.0 software (http://surfer.nmr.mgh.harvard.edu/) by applying the default preprocessing pipeline for cortical reconstruction and volumetric segmentation. A quality control protocol was then conducted over the FreeSurfer segmentations with the Freeview program. FreeSurfer segmentations were visually inspected on a slice-by-slice basis by an experienced technician, to enhance the reliability of interpretation. Finally, FreeSurfer outputs were entered into the Normative Morphometry Image Statistics (NOMIS) software (https://github.com/medicslab/NOMIS) [34] to estimate the Z scores of each volumetric measure adjusted for age, sex and intracranial volume. NOMIS is a comprehensive tool built upon a large MRI dataset comprising 6909 cognitively healthy individuals aged 18 to 100 years. Participants with SCD and with adjusted Z scores in the left and/or right hippocampal volume below one standard deviation were categorized as SCD+. The cut-off value of $Z < -1.0$ used to determine the presence of prominent hippocampal atrophy was selected on the basis of previous findings [11].

CU participants showed normal general cognitive performance, tested by the Spanish version [40] of the Cambridge Cognitive Assessment – Revised battery (-CAMCOG-R- [41] according to age and education norms [33]) and did not meet the SCD criteria described above. In addition, all CU and SCD- participants had normal hippocampal volumes adjusted for age, sex and intracranial volume.

Participants gave their written informed consent prior to taking part in the study. The research project was approved by the Galician Clinical Research Ethics Committee (Xunta de Galicia, Spain; Refs. 2017/498; 2022/116) and was performed in accordance with the ethical standards established in the Declaration of Helsinki.

Standard CONN toolbox pre-processing pipeline was employed, and it is described along acquisition parameters thoroughly in Appendix published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics.

Seed-based connectivity analysis (SBA)

To evaluate intergroup differences (CU, SCD-, and SCD+) in the functional connectivity of the DMN, we used predefined DMN regions of interest (ROIs) from the network atlas incorporated in CONN. These DMN nodes encompassed the Precuneus cortex, right and left lateral parietal cortex (LPC), and medial prefrontal cortex (mPFC) seeds (the functional nodes were obtained by independent component analysis of a dataset from the Human Connectome Project, see the CONN website for additional details).

We applied a General Linear Model (GLM) with a hemodynamic response function (HRF) weighting at the first level, which corresponds to the within-subject analysis. Specifically, this step involved computing the standard bivariate correlation between the time series of the seed region and the rest of the brain, generating individual functional connectivity maps for each participant and seed.

At the second level, a group-level analysis was conducted to examine differences in functional connectivity across groups (SCD-, SCD+, and controls). Statistical significance was assessed using a threshold of $p < 0.05$, false discovery rate (FDR) cluster-level corrected for multiple comparisons, in combination with a threshold of $p < 0.001$ at the uncorrected voxel level.

All seed-based statistical analyses were conducted under the parametric assumptions of random field theory [38].

We included age and years of formal education as no-interest covariates in all statistical analyses. The automated anatomical atlas 3 (AAL3) was used for anatomical reference [39].

Table 1
Mean values and standard deviations (SD, in brackets) of demographic and neuropsychological measures.

	CU $N = 69$	SCD- $N = 51$	SCD+ $N = 13$	p *	Post hoc comparison
Age	63.19 (8.41)	66.49 (8.98)	72.31 (7.28)	.0013	.038[a]/ < .001[b]/.03[c]
Years of education	13.16 (5.80)	10.20 (4.95)	10.53 (4.96)	.010	.004[a]
Gender (male/female)	14 / 55	15 / 36	5 / 8	.281[1]	NS
QAM	14.87 (1.93)	19.55 (2.12)	18.77 (1.79)	< .001	< .001[a]/ < .001[b]
General Cognitive Functioning					
MMSE	28.49 (1.56)	28.47 (1.54)	27.61 (1.66)	.174	NS
Attention					
TMT-A (seconds)	47.64 (23.71)	50.71 (22.76)	49.02 (22.62)	.760	NS
CAMCOG-R (Attention and Calculation)	7.77 (1.55)	7.73 (1.25)	7.46 (1.51)	.781	NS
Executive Function					
TMT-B (seconds)	120.99 (77.28)	134.88 (65.76)	132.23 (42.69)	.553	NS
CAMCOG-R (Executive Function)	21.93 (3.88)	21.76 (11.37)	18.54 (4.18)	.336	NS
Memory					
CVLT (Immediate free recall)	53.86 (9.11)	52.29 (9.71)	47.15 (8.61)	.059	.018[b]
CVLT (Short-delay free recall)	11.30 (2.70)	10.59 (2.69)	10.54 (3.31)	.319	NS
CVLT (Long-delay free recall)	12.04 (2.63)	11.74 (2.24)	10.69 (3.01)	.209	NS
CAMCOG-R (Memory)	22.88 (2.36)	21.94 (2.62)	21.38 (1.85)	.035	.037[a]/.043[b]
Language					
BNT	51.20 (7.62)	50.78 (7.35)	47.92 (6.09)	.342	NS
CAMCOG-R (Language)	27.58 (1.83)	26.63 (2.18)	25.69 (2.40)	.002	.012[a]/.003[b]
Depression					
Geriatric Depression Scale − 15	2.41 (2.46)	3.10 (2.13)	2.67 (2.32)	.246	NS

Abbreviations: CU: control unimpaired group, SCD-: subjective cognitive decline without hippocampal atrophy of AD, SCD+ : subjective cognitive decline with hippocampal atrophy. Post-hoc comparisons: ***a*:** CU *vs* SCD-; ***b***: CU *vs* SCD+ ; ***c***: SCD- *vs* SCD+ ; * ANOVA p value; * Chi-square p value[1]; QAM: Questionnaire d'auto-évaluation de la Mémoire; MMSE: Mini-Mental State Examination; CVLT: California Verbal Learning Test, CAMCOG-R: Cambridge Cognitive Examination -Revised; BNT: Boston Naming Test; TMT: Trail Making Test; NS: not significative

Partial correlation and dynamic independent component analysis

For insight into the SBA findings related to the higher anti-correlations (i.e. negative connectivity) between the right LPC of the DMN and regions associated with task-positive networks, as observed in the SCD+ group relative to both the SCD- and CU groups, post-hoc partial correlations were determined. The correlations between the cluster derived from the F test for the right LPC seed that showed greater differences across groups (see Supplementary Table 1 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics) and the executive function scores derived from the CAMCOG for each of the groups were controlled for the variables sex, formal education, age and scores on the geriatric depression scale. Executive function scores were chosen because the cluster that yielded the most significant differences included regions linked to attentional networks, specifically the dorsal attention network (DAN) and the fronto-parietal control network (FPCN) [49]. Given the competitive interaction between the DMN and task-positive attentional networks [17,42,6], we hypothesized that the increased dominance of the DMN observed in the SCD+ group (characterized by stronger anti-correlations and a higher frequency of DMN activation at the expense of task-related networks) could interfere with attentional network functioning.

To test this hypothesis, we focused on a single executive function measure and performed three separate comparisons (one for each group: SCD-, SCD+, and controls). Accordingly, Bonferroni correction was applied to account for these three comparisons.

Furthermore, Dynamic Independent Component Analysis (Dyn-ICA) was used to assess the temporal dynamics of the DMN, by considering the cortical ROIs derived from the network atlas included in CONN (see a complete description in Appendix published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics).

We focused on the temporal aspects (frequency and variability) of the target circuit (see [1] for a similar approach). Frequency indicates activation recurrence of a certain circuit, while variability is explained by the standard deviation of the temporal component across time series and subjects [30].

Results

Seed-based connectivity analysis

Overall, the results revealed significant differences in functional connectivity patterns among the study groups (CU, SCD-, and SCD+), particularly within the DMN. Both the SCD- and SCD+ groups exhibited greater functional connectivity within the DMN compared to CU participants, with the effect being more pronounced in SCD+. Additionally, higher levels of anti-correlation were observed in SCD+ relative to both CU and SCD- participants, specifically involving the right LPC DMN seed and bilateral parietal regions.

Concretely, significant differences in seed-to-voxel connectivity across groups (CU, SCD-, SCD+) were observed for right and left LPC DMN ROIs (see Supplementary Table 1 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics). Left and right LPC one-samples t-tests and seeds are shown in Supplementary Figure 1 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics.

Relative to the SCD- group, the SCD+ group exhibited more functional connectivity between the left LPC seed and frontal regions: left supplementary motor area and bilateral superior frontal gyrus (see Table 2 and Fig. 1a). The SCD+ group also showed greater connectivity than the CU group between the left LPC seed and left frontal region (specifically, the supplementary motor area, middle frontal gyrus, and superior frontal gyrus) and right temporo-occipital region (middle temporal gyrus and middle occipital gyrus) of the DMN (see Table 2 and Fig. 1b).

For the right LPC seed, as observed for the left LPC seed, relative to the CU group, the SCD+ group exhibited greater functional connectivity with frontal regions (left middle frontal gyrus, bilateral superior frontal gyrus, left inferior frontal gyrus and right supplementary motor area) and with the middle temporal gyrus extending to the angular gyrus and middle occipital gyrus in the right hemisphere (see Table 3 and Fig. 2a). Additionally, SCD- participants exhibited greater functional connectivity in left middle and superior frontal gyrus for the right LPC seed than the CU group (see Table 3 and Fig. 2b).

Table 2
Brain regions that showed significant functional connectivity differences in the SBA between-group analyses of the left lateral parietal cortex seed.

Brain region	L/R	Cluster size	# voxels in specific region (% overlap)	MNI Coordinates (x,y,z)			T-value
SCD + > SCD-							
Supplementary motor area	L	240	147 (7)	−10	10	56	4.34
Superior frontal gyrus, medial part	L		53 (2)				
Superior frontal gyrus, medial part	R		25 (1)				
SCD + > CU							
Supplementary motor area	L	429	171 (8)	−8	10	58	4.39
Middle frontal gyrus	L		104 (2)				
Superior frontal gyrus	L		88 (2)				
Superior frontal gyrus, medial part	L		37 (1)				
Middle temporal gyrus	R	278	220 (5)	56	−70	16	4.35
Middle occipital gyrus	R		38 (2)				

Keywords: L/R: Left or right hemisphere; **Cluster size**: numbers of voxels in each cluster; **MNI**: Montreal Neurological Institute coordinates. **CU**: control unimpaired group; **SCD-**: subjective cognitive decline without hippocampal atrophy; **SCD +**: subjective cognitive decline with hippocampal atrophy. Results are significant at $p < 0.05$ FDR cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level. Only data on brain regions with > 1 % cluster overlap are shown.

Additionally, different effects were observed for the right LPC in the SCD + group than in the CU and SCD- groups. Relative to the SCD + group, the CU group showed heightened functional connectivity encompassing bilateral brain regions such as the postcentral and precentral gyrus, superior/inferior parietal gyrus, precuneus, supplementary motor area, paracentral lobules and superior frontal gyrus, along with the right middle cingulate gyrus. The higher connectivity in CU participants was explained by higher anti-correlations in the SCD + (see Table 3 and Fig. 2c). Finally, relative to the SCD + group, the SCD- group exhibited greater functional connectivity of the right LPC with two large clusters extending almost symmetrically through the bilateral postcentral, inferior/superior parietal gyrus, precuneus, right paracentral and left supramarginal gyrus; these results are explained by higher anti-correlations in the SCD + group than in the SCD- group (see Table 3 and Fig. 2d).

Correlation analysis

The connectivity values for the right LPC and the cluster of parietal regions derived from the F test were significantly associated with the connectivity values of the right LPC and the cluster of parietal regions derived from the F test (MNI peak coordinates −32, −42, 48; see Supplementary Table 1 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics) with the executive function scores of the CAMCOG only for the SCD + group ($r = 0.793$, $p = 0.011$). This association remained significant after Bonferroni correction for multiple comparisons ($p = 0.033$).

Dyn-ICA

To shed light on the higher anti-correlations between the right LPC node of the DMN and parieto-central regions in the SCD + group than in the CU and SCD- groups, we examined the temporal aspects of the specific circuit corresponding to DMN activation and deactivation of task-positive networks (see Supplementary Figure 2 published as supplementary material online attached to the electronic version of this paper at https://www.cambridge.org/core/journals/international-psychogeriatrics).

A marginal significant group effect was only observed for the activation frequency parameter of this circuit $F(2, 128) = 3.00$, $p = 0.0533$. Specifically, the SCD + group exhibited a higher frequency of use of this circuit than in both the CU group ($T(128) = 2.07$ $p = 0.0202$) and the SCD- group ($T(128) = 2.45$ $p = 0.0079$).

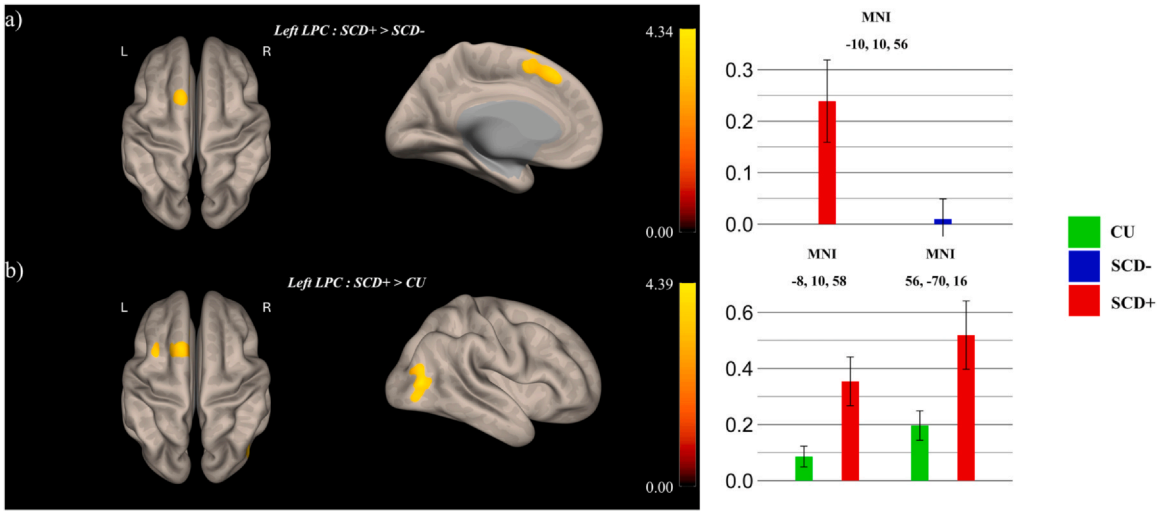

Fig. 1. Significant differences in brain connectivity obtained through the SBA of the left lateral parietal cortex seed, where the colored bars represent t-scores of the clusters (**left**). Mean z-scores values derived from the significant clusters; the error bars represent the 95 % confidence interval. For graphs with more than one cluster, peak MNI coordinates are specified (**right**). Results are significant at $p < 0.05$ FDR cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level.

Table 3
Brain regions showing significant functional connectivity differences in the SBA between-group analyses of the right lateral parietal cortex seed.

Brain region	L/R	Cluster size	# voxels in specific region (% overlap)	MNI Coordinates (x,y,z)			T-value
SCD + > CU							
Middle temporal gyrus	R	424	190 (4)	46	−74	36	4.54
Angular gyrus	R		94 (5)				
Middle occipital gyrus	R		54 (3)				
Middle frontal gyrus	L	295	189 (4)	−34	16	60	4.46
Superior frontal gyrus	L		78 (2)				
Superior frontal gyrus	R	195	103 (2)	16	28	52	3.97
Superior frontal gyrus, medial part	R		69 (3)				
Supplementary motor area	R		16 (8)				
Middle frontal gyrus	L	190	148 (3)	−46	18	38	4.74
Inferior frontal gyrus	L		42 (4)				
SCD- > CU							
Middle frontal gyrus	L	212	109 (2)	−26	24	60	4.73
Superior frontal gyrus	L		82 (2)				
CU > SCD +							
Postcentral gyrus	L	1696	534 (14)	−26	−44	62	4.71
Superior parietal gyrus	L		242 (12)				
Precuneus	L		239 (7)				
Precentral gyrus	L		222 (6)				
Paracentral lobule	L		138 (10)				
Inferior parietal gyrus	L		69 (3)				
Supplementary motor area	L		56 (3)				
Superior frontal gyrus	L		40 (1)				
Precuneus	R	870	232 (7)	12	−48	58	4.62
Postcentral gyrus	R		227 (6)				
Superior parietal gyrus	R		218 (10)				
Paracentral lobule	R		43 (5)				
Inferior parietal gyrus	R		22 (2)				
Middle cingulate gyrus	R		12 (1)				
Superior frontal gyrus	R	311	125 (2)	18	−14	66	4.14
Supplementary motor area	R		83 (4)				
Middle cingulate gyrus	R		83 (4)				
Precentral gyrus	R		17 (1)				
SCD- > SCD +							
Postcentral gyrus	L	1242	451 (12)	−32	−44	52	4.94
Inferior parietal gyrus Precuneus	L		268 (11)				
	L		227 (6)				
Superior parietal gyrus	L		180 (9)				
Supramarginal gyrus	L		7 (1)				
Superior parietal gyrus	R	683	186 (8)	24	−52	52	4.49
Precuneus	R		142 (4)				
Inferior parietal gyrus	R		70 (5)				
Postcentral gyrus	R		56 (1)				
Paracentral lobule	R		42 (5)				

Keywords: L/R: Left or right hemisphere; **Cluster size**: numbers of voxels in each cluster; **MNI**: Montreal Neurological Institute coordinates; **CU**: control unimpaired group; **SCD-**: subjective cognitive decline without hippocampal atrophy; **SCD +** : subjective cognitive decline with hippocampal atrophy. Results are significant at $p < 0.05$. FDR cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level. Only brain regions with > 1 % cluster overlap are presented.

Discussion

The objective of the present exploratory study was to determine whether participants with SCD, particularly those with a neuro-structural marker of risk for AD (i.e. hippocampal atrophy; SCD +), exhibit differences in the functional connectivity of the DMN relative to a control group and to a SCD- group, as this network is known to be altered in individuals in prodromal and clinical stages of the AD continuum. We used whole-brain seed-based analysis to assess intrinsic and extrinsic functional connectivity of the DMN. Additionally, we correlated the findings with neuropsychological data and used Dyn-ICA to examine temporal aspects of the DMN for a better understanding of our results.

The results showed that SCD is associated with objective alterations in DMN functional connectivity, despite the lack of objective cognitive impairment. Both SCD + and SCD- participants showed greater connectivity between the right LPC seed and frontal regions than CU participants. These findings add to the body of literature suggesting that increases in DMN functional connectivity is related to SCD, regardless of whether any distinction is made regarding the risk of AD [14,18,31,43,7].

However, in the present study, individuals with SCD + exhibited stronger and more widespread hyperconnectivity than individuals with SCD-. Specifically, comparison of the SCD + group and the CU group revealed increased DMN connectivity in the right temporo-occipital region (for the left LPC seed) and parieto-temporal-occipital regions (for the right LPC seed), which are linked to autobiographical memory recall (middle temporal gyrus [20]), episodic buffer by combining auditory and visual data with long-term memory necessary for conscious processing (angular gyrus [44]) and referential processing (middle occipital gyrus [24]).

Further comparison revealed significantly greater connectivity of the left LPC seed and anterior DMN brain regions, including the left supplementary motor area and bilateral superior frontal gyrus in the SCD + group than in the SCD- group. Similarly, greater functional connectivity between the left LPC seed and the left frontal DMN brain regions, specifically the supplementary motor area, middle frontal gyrus and superior frontal gyrus was observed in the SCD + group than the CU group. While the supplementary motor area is primarily associated with the somato-motor network, it has also been associated with the DMN in the context of aging [37] and with mind wandering [19].

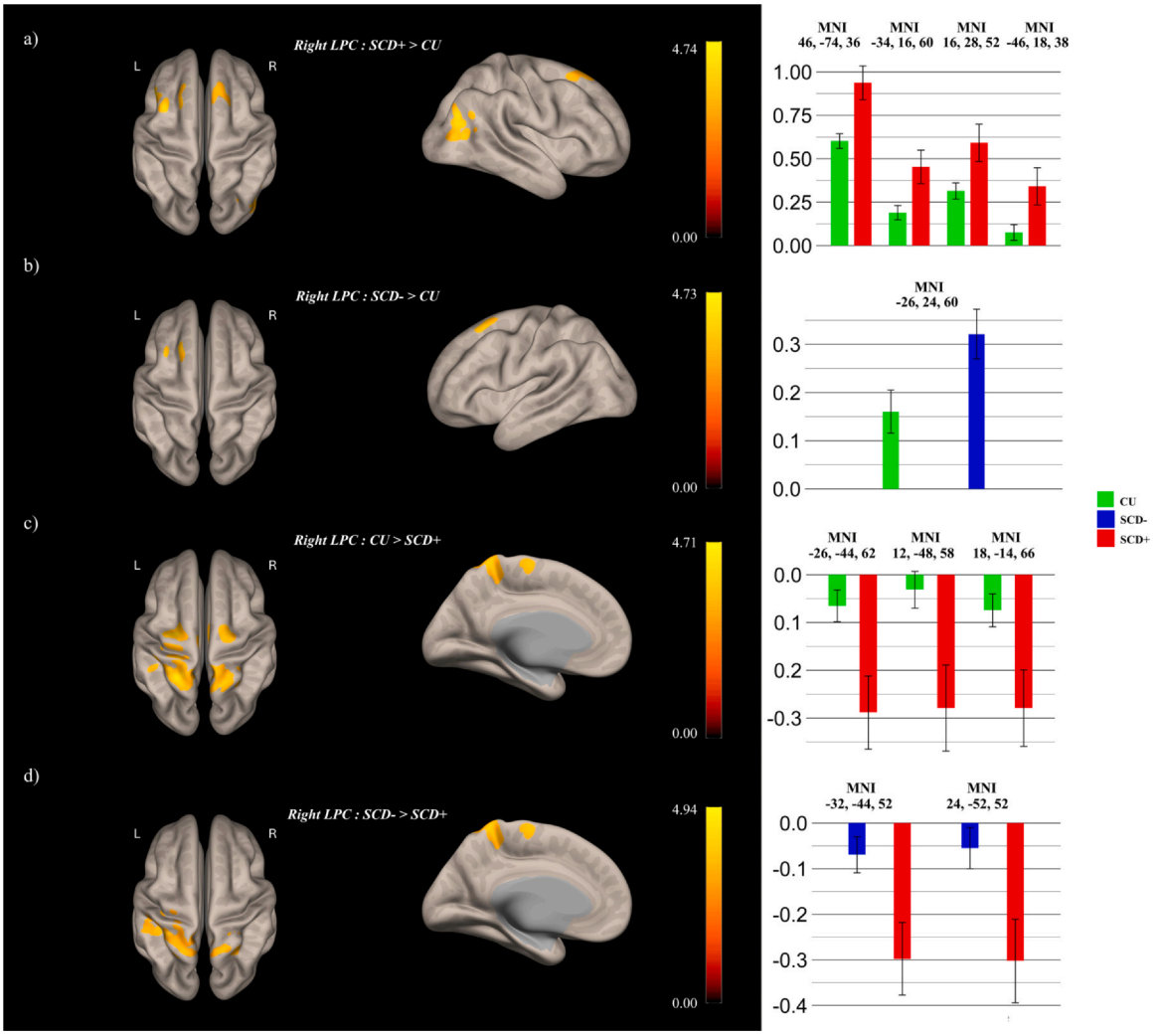

Fig. 2. Significant differences in brain connectivity obtained through the SBA of the right lateral parietal cortex seed; the colored bars represent t-scores of the clusters (**left**). Mean z-scores values derived from the significant clusters; the error bars represent the 95 % confidence interval. For graphs with more than one cluster, peak MNI coordinates are specified (**right**). Results are significant at $p < 0.05$ FDR cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level.

Furthermore, the right LPC seed showed greater connectivity with widespread bilateral frontal DMN regions in the SCD + group than in the CU group, including the supplementary motor area, the superior frontal gyrus and the left middle frontal gyrus extending to the inferior frontal gyrus, brain regions linked to mind wandering (middle frontal gyrus and supplementary motor area [19]) and self-referential processing (inferior and superior frontal gyrus [15,28]).

A previous study investigating functional connectivity in patients with amnestic mild cognitive impairment (aMCI) found a hyperconnectivity pattern in the DMN, similar to the SCD + group in the present study in frontal and temporo-occipital regions [26]. Moreover, another study observed hyperconnectivity between posterior DMN nodes and frontal regions in AD dementia, which was linked to amyloid burden [23]. These findings suggest that both SCD groups may be situated along the AD continuum; however, compared with SCD-, SCD + appears to be a step further along the continuum. Interestingly, the right LPC seed indicated a different effect for the SCD + group, than for the SCD- and CU groups, with higher anti-correlations between the right LPC seed and parieto-central regions associated with task-related networks, mainly related to attentional and somato-motor networks [49].

Most of the existing literature indicates a decline in levels of anti-correlation between the DMN and task networks in the context of healthy aging and MCI, indicating the anti-correlation as a reflection of the brain's inherent functional organization and optimal cognitive state [17]. However, a recent study observed a similar effect associated with the MCI diagnosis to that observed in the present study for the SCD + group [25]. The previous study, in which participants were classified as Control, SCD or MCI, found that the MCI participants exhibited greater anti-correlation between the LPC of the DMN and the supramarginal gyrus, a region linked to task networks [25]. The higher levels of anti-correlation observed in the SCD + group with parietal regions linked to task-related networks are similar to those observed in the MCI group in the previously mentioned study [25], suggesting that the SCD + group may be within the AD continuum.

To better understand the anti-correlations, we conducted a partial correlation analysis between the cluster associated with anti-correlation between the DMN right LPC and parietal regions, which yielded the strongest statistical effect, with the executive function scores of the groups. We also conducted a Dyn-ICA to explore the temporal dynamics of DMN activation in conjunction with task-related network deactivation. Only the SCD + group showed a statistically significant association between functional connectivity values and executive function scores, showing a positive correlation between these variables.

The Dyn-ICA analysis revealed that SCD + group showed higher activation frequency in the target circuit than CU and SCD- groups, which may be related to increased anti-correlations between the right

LPC and centro-parietal regions observed in static functional connectivity analyses, although it is important to note that the F test across groups for the frequency metric was marginally significant ($p = 0.053$).

The statistical trend regarding the heightened connectivity with the DMN in the SCD+ group relative to the CU and SCD- groups may be related to the higher levels of anti-correlation observed in the SCD + relative to both SCD- and CU groups, and may interfere with the interaction between the DMN and task-related networks, given the well-established antagonistic relationship between these networks [17,42,6]. In a previous study, a comparable effect on dynamic activation was observed in SCD participants for a similar neural circuit. However, no objective criteria indicating AD risk were applied to characterize the sample in that study [8].

Hippocampal atrophy is considered a risk factor in the development of AD in the SCD+ group, and previous findings suggest an initial disinhibitory process originating in the medial temporal lobe, which directly extends to the posterior nodes of the DMN in the prodromal state of the disease [23]. The observed outcomes, such as heightened functional connectivity within the DMN, increased the anti-correlations between the right LPC and centro-parietal regions of task-related networks and the negative link with executive functioning. Together with the results of Dyn-ICA analyses comparing the SCD+ group with both CU and SCD- groups, these observations suggest a disinhibitory process within the DMN, leading to enhanced recurrence to this network at the expense of task-positive networks [17,42,6]. Importantly, this hypothetical functional disinhibition could contribute to increased degeneration over time [23].

In line with the interpretation of a non-compensatory mechanism associated with DMN hyperconnectivity or DMN disinhibition, administration of low doses of antiepileptics in aMCI, leading to reduced hippocampal activity, has been reported to result in cognitive improvement [2]. Furthermore, hyperconnectivity of the DMN has been found to be negatively associated with neuropsychological scores in MCI subjects [29]. Moreover, a previous study observed a reduction in hyperconnectivity within the DMN that was associated with cognitive improvement in a population of aMCI participants [12].

This study has two main limitations. The first is the cross-sectional nature of the experimental design. The second is the relatively small sample size, particularly in the SCD+ group. This limitation is due to the specific and challenging nature of recruiting participants with this profile. Our research group is actively working to expand the sample, and we hope to include a greater number of SCD+ participants in future studies to strengthen the robustness of our findings. Future studies should also evaluate conversion rates to MCI and AD longitudinally in larger samples of both SCD- and SCD+ groups, while also examining associations with other established AD-related biomarkers.

In summary, the present findings suggest that hyperconnectivity within the DMN may serve as a potential objective marker for subjective cognitive complaints, as the effect was more prevalent in both the SCD+ and SCD- groups than in the CU group. However, the SCD + group exhibited a pattern similar to that of later stages on the AD continuum regarding DMN hyperconnectivity and increased anti-correlations between DMN and task-positive network regions, supporting the idea that hippocampal atrophy could be evaluated to improve the characterization of SCD linked to AD and provide a potential description of the neurofunctional changes of the DMN in the AD continuum. These findings also suggest potential targets for intervention in preclinical AD, focusing on reducing DMN hyperconnectivity and strengthening attentional networks antagonistic to this network.

CRediT authorship contribution statement

Mónica Lindín: Writing – review & editing, Resources, Project administration, Funding acquisition. **Montserrat Zurrón:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Miguel Ángel Rivas-Fernández:** Writing – review & editing, Writing – original draft, Formal analysis. **Benxamín Varela-López:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Santiago Galdo-Álvarez:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization. **Fernando Díaz:** Writing – review & editing, Resources, Project administration, Funding acquisition.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.inpsyc.2025.100067.

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