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RESEARCH ARTICLE

Altered limbic functional connectivity in individuals with subjective cognitive decline: Converging and diverging findings across Chinese and German cohorts

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Abstract

INTRODUCTION: It remains unclear whether functional brain networks are consistently altered in individuals with subjective cognitive decline (SCD) of diverse ethnic and cultural backgrounds and whether the network alterations are associated with an amyloid burden.

METHODS: Cross-sectional resting-state functional magnetic resonance imaging connectivity (FC) and amyloid-positron emission tomography (PET) data from the Chinese Sino Longitudinal Study on Cognitive Decline and German DZNE Longitudinal Cognitive Impairment and Dementia cohorts were analyzed.

RESULTS: Limbic FC, particularly hippocampal connectivity with right insula, was consistently higher in SCD than in controls, and correlated with SCD-plus features.

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Smaller SCD subcohorts with PET showed inconsistent amyloid positivity rates and FC–amyloid associations across cohorts.

DISCUSSION: Our results suggest an early adaptation of the limbic network in SCD, which may reflect increased awareness of cognitive decline, irrespective of amyloid pathology. Different amyloid positivity rates may indicate a heterogeneous underlying etiology in Eastern and Western SCD cohorts when applying current research criteria. Future studies should identify culture-specific features to enrich preclinical Alzheimer's disease in non-Western populations.

KEYWORDS
amyloid deposition, Centiloid, cross-cultural harmonization, functional connectivity, hippocampus, insula, subjective cognitive decline

Highlights

- Common limbic hyperconnectivity across Chinese and German subjective cognitive decline (SCD) cohorts was observed.
- Limbic hyperconnectivity may reflect awareness of cognition, irrespective of amyloid load.
- Further cross-cultural harmonization of SCD regarding Alzheimer's disease pathology is required.

1 | BACKGROUND

Subjective cognitive decline (SCD), a status in individuals of higher age with perceived cognitive decline without objective evidence for impairments on standardized cognitive tests, has been considered promising for early detection of Alzheimer's disease (AD).[1,2] Recently, SCD was recognized as a clinical indicator for the cognitive transition stage of the AD continuum, that is, between fully normal cognition and objectively detectable cognitive impairment.[3] Despite commonly observed increases in rates of incident AD dementia,[4] amyloid positivity rates vary considerably depending on specific sample characteristics.[5] For enrichment of preclinical AD, additional SCD-plus criteria, such as concerns regarding cognitive decline, were proposed.[1,2]

The SCD concept was mainly driven by research in Western cohorts.[1,2,5] SCD assessment does not rely on objective performance measures, but essentially on self-reports, which may be affected by language and cultural backgrounds.[1] Cultural factors, such as social stigmatization of cognitive problems, responding style on self-reported measures, and tolerance of slowly progressive cognitive decline in aging,[6] may influence the willingness and accuracy of self-reports on cognitive decline. Accordingly, it is unclear whether the current SCD research definition is equally suited for Eastern populations, or needs tailoring regarding cultural appropriateness and specificity for the target population.[7] To harmonize SCD research across cultures, Sino-German conferences took place (2016, 2017, 2019),[8] and Chinese SCD cohorts were established using a contemporary SCD research definition.[9–12] Beyond adherence to the general SCD definition, various SCD-related features[1,2] were coded, and their predictive value for amyloid burden was tested in Chinese SCD subjects.[13,14] Still, comparability between SCD individuals from both countries is unknown.

During a neurodegenerative process, the brain undergoes alterations from abnormally aggregated proteins and changes in neuronal networks to behavioral and cognitive symptoms.[15,16] Neuronal networks involving key limbic areas are particularly interesting in view of their critical role in processing emotions, memories, and other cognitive functions.[17] Limbic network alterations were previously observed along the AD continuum,[18–20] including SCD populations.[21] Beyond incipient atrophic[22,23] and hypometabolic alterations[24,25] in limbic areas, changes in network function at wakeful rest were frequently reported in SCD, although with conflicting results.[26] Both increases,[22,27–31] decreases,[32–35] and no differences[36] in functional connectivity (FC) involving key limbic areas were observed in SCD compared to cognitively normal controls (NC). Reasons for inconsistencies could be small sample sizes,[32] heterogeneous SCD definitions,[22,36] and divergent analytical techniques, such as seed-based approaches,[29] independent component analysis,[36] or topological network properties.[30] Furthermore, ethnicity can be an additional source of variance for functional network organization.[37,38]

There is also limited evidence regarding whether changes of limbic FC in SCD are related to brain amyloid burden. Higher amyloid burden was associated with decreased seed-based functional connectivity (sFC) between basal forebrain and limbic areas (i.e., hippocampus and thalamus),[39] increased sFC between the precuneus and

occipital regions,[40] and increased topological network properties within the default mode network (DMN).[30] A longitudinal study showed widespread increased FC within the DMN 24 months after baseline measurements. However, this was not modulated by baseline amyloid positivity.[41] Importantly, previous studies have not systematically examined whether amyloid burden–related FC changes are generalizable across ethnically diverse SCD samples.

For these reasons, the current study aimed at investigating FC between key limbic structures and the rest of the brain in two independent but similarly conceptualized SCD cohorts from Germany and China. FC changes in SCD with different ethnic and cultural backgrounds were evaluated using identical FC analytic approaches. Two complementary voxel-wise connectivity measures served as readouts of functional brain networks, a graph-based approach (i.e., weighted degree of connectivity [DC]) and a seed-based method (sFC). Weighted DC provides precise centrality characterization of functional brain networks and allows unbiased exploration of regions with abnormal global connectivity. The sFC estimates the interregional connectivity strength for characterizing the underlying mechanism of altered network integration for a specific brain region.[42,43] Therefore, this cross-ethnic study allowed us to determine (1) common limbic FC changes associated with SCD, regardless of ethnicity, and (2) distinct limbic FC changes associated with SCD specific to each ethnic cohort. Finally, (3) in SCD participants with available amyloid positron emission tomography (PET) data, relationships between limbic FC changes and cortical amyloid load were examined in each cohort separately.

RESEARCH IN CONTEXT

1. **Systematic Review**: Accumulating evidence points toward aberrant limbic functional connectivity (FC) in subjective cognitive decline (SCD). The establishment of the current research framework of SCD is based on Western populations. Translation to other cultural contexts is still pending.
2. **Interpretation**: Limbic FC is consistently elevated in two large SCD cohorts from different ethnic and cultural backgrounds, suggesting common early brain network adaptations that may reflect an increased awareness of cognitive decline, not driven by amyloid pathology. Current cohort differences in brain amyloid burden may indicate a heterogeneous etiology in SCD defined by the current research definition, which may underlie the diverse functional reorganization between these two cohorts.
3. **Future Directions**: Further harmonizing the SCD concept across borders and cultures is necessary. Future work should identify culturally specific SCD features to achieve enrichment of preclinical Alzheimer's disease and guide future treatment and prevention in non-Western populations.

2 | METHODS AND MATERIALS

The current analysis included data from two independent studies, SILCODE (Sino Longitudinal Study on Cognitive Decline) from China and DELCODE (DZNE Longitudinal Cognitive Impairment and Dementia) from Germany: both are ongoing longitudinal observational studies aiming to diagnose, estimate, and predict cognitive decline in SCD subjects using multimodal data, including clinical information, neuropsychological assessments, biological markers, and neuroimaging.[9,43,44]

2.1 | Subjects

SCD groups in both cohorts were defined by self-perceived continuous cognitive decline compared to a previous normal state unrelated to an acute event, not meeting the criteria for mild cognitive impairment or dementia (see supporting information). In both cohorts, at least one essential SCD-plus criterion (i.e., concerns related to SCD) had to be met for inclusion. NC groups in both cohorts were within the normal range on cognitive tests and reported no self-perceived cognitive declines of concern. We selected SILCODE subjects aged ≥ 60 years to better comply with the inclusion criteria of DELCODE. All DELCODE SCD subjects were referred from memory clinics. SILCODE SCD subjects were partially recruited from memory clinics and advertisements.

The current analyses included baseline data of 218 SILCODE subjects ($SILCODE_{whole}$) and 531 DELCODE subjects ($DELCODE_{whole}$; Figure 1A) after magnetic resonance (MR) quality controls (MRIQC;[45] Figure S1; Tables S1, S2 in supporting information). In $SILCODE_{whole}$, $n = 68$ (57%) SCD were recruited from memory clinics. Amyloid-PET was available in 59 SILCODE SCD subjects ($SILCODE_{PET}$: $n = 39$ [66%] from memory clinics) and 59 DELCODE SCD subjects ($DELCODE_{PET}$). Both studies were approved by the responsible ethics committees and radiation protection authorities.[9,43] All participants provided written informed consent.

2.2 | Clinical and neuropsychological assessments

All subjects underwent cohort-specific standardized neuropsychological assessment probing episodic memory, executive function, and language, performing in the normal range at baseline.[44,46,47] Both cohorts applied the Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS),[48,49] and structured Subjective Cognitive Decline Interview (SCD-I).[44,50] Based on SCD-I, we summarized the number of SCD cognitive domains (SCD-domain) and the number of features potentially associated with an increased risk of cognitive decline in SCD (SCD-plus).[1,2] The latter includes (1) perceived decline in the memory domain, (2) onset of SCD within the last 5 years in persons aged over 60 years, (3) SCD-related concerns, and

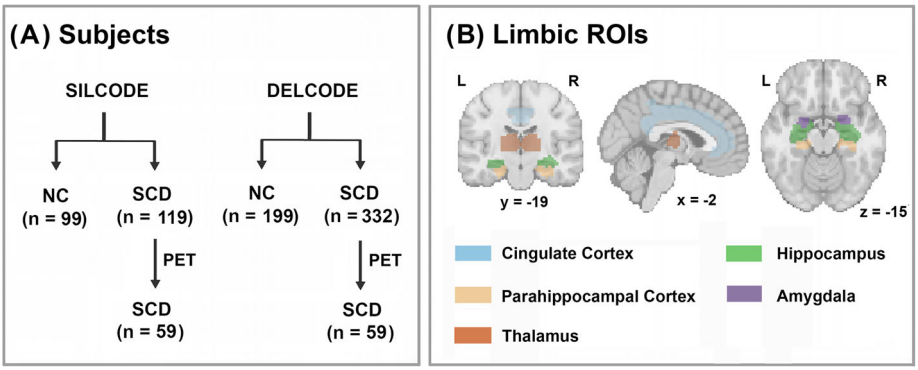

FIGURE 1 Sample size and seed regions for the functional connectivity analyses. A, The number of subjects in each cohort and subcohort with amyloid PET. B, Illustration of the masks for the limbic ROIs derived from the Automated Anatomical Labeling atlas.[54] The cingulate ROI encompasses the anterior, middle, and posterior parts of the cingulate cortex. The composite-limbic ROI mask is composed of all limbic ROIs. L, left; NC, normal controls; PET, positron emission tomography; R, right; ROI, region of interest; SCD, subjective cognitive decline.

(4) feeling cognitively worse than peers. We omitted the feature informant confirmation[50] due to insufficient data in $SILCODE_{whole}$. We also report cohort-specific measures on episodic memory (SILCODE: Adult Verbal Learning Test [AVLT];[51] DELCODE:a composite memory score [MEM][47]), and anxiety symptoms (SILCODE: Hamilton Anxiety Rating Scale [HAMA];[52] DELCODE: Geriatric Anxiety Inventory–Short Form [GAI-SF][53]). Apolipoprotein E (*APOE*) genotype was obtained from both cohorts (see supporting information).

2.3 | MR and PET imaging

2.3.1 | Image acquisition

SILCODE magnetic resonance imaging (MRI) data were acquired with a single 3T scanner. DELCODE is a multicenter study with scanning protocols harmonized across 3T scanners of participating sites. Technical details for the T1-weighted anatomical and resting-state functional MRI (rs-fMRI) scans are presented in Table S3 in supporting information.

Amyloid-PET examinations were performed with ^{18}F-florbetapir (FBP, Eli Lilly) in SILCODE and ^{18}F-florbetaben (FBB, Life Radiopharma) in DELCODE at the nuclear medicine departments of the participating sites (for details see Table S4 in supporting information).

2.3.2 | Pre-processing of MRI data

Pre-processing of structural and rs-fMRI data was performed using SPM12, including motion correction, slice time correction, coregistration, normalization, detrending, smoothing, nuisance regression (motion, white matter, cerebrospinal fluid signals), and temporal bandpass filtering (0.01-0.1 Hz; see supporting information).

2.3.3 | Assessment of limbic FC

Masks for key limbic regions of interest (ROI; Figure 1B), including bilateral cingulate cortex, hippocampus, parahippocampal cortex, amygdala, and thalamus, were created from the Automated Anatomical Labeling (AAL) atlas.[54] All limbic ROIs were also combined into a composite-limbic ROI mask.

DC values were calculated using GRETNA[55] at voxel level by quantifying the sum of the connectivity weights within a whole brain mask encompassing both limbic and non-limbic areas. The mean DC values within each limbic ROI[55,56] were standardized within each cohort (standard DC). It provides a global characterization of the importance of ROIs in the overall brain network[56] (Table S5 in supporting information).

sFC was calculated using GRETNA by assessing interregional connectivity between each limbic AAL ROI seed and the rest of the brain.[33,35,40] Here, the mean time series of each limbic ROI was correlated with each voxel of the entire brain to obtain the sFC maps, which were Fisher *z* transformed.

2.3.4 | PET Centiloid analyses

Cortical tracer binding of FBP in $SILCODE_{PET}$ and FBB in $DELCODE_{PET}$ was quantified using the Centiloid method[57] to derive standardized analyses of global cortical amyloid burden. $SILCODE_{PET}$ FBP data were analyzed in SPM12, while $DELCODE_{PET}$ FBB data were analyzed with PMOD 4.2 (PMOD Technologies LLC), after calibration using the validation datasets (see supporting information). To indicate early amyloid positivity, Centiloid ≥20 was used based on recent suggestions.[58]

2.4 | Statistical analysis

2.4.1 | Sample characteristics

Across the two cohorts, two-way analyses of variance (ANOVA) with cohort and group as main factors or chi-square tests were carried out for sample characteristics. For those variables that were only available for one cohort, two-sample *t* tests were performed to assess group differences within each cohort. Two-sample *t* tests or chi-square tests were applied for the SCD-only PET subcohorts to measure cohort

differences in sample characteristics and Centiloid values. A $P < 0.05$ was considered significant for all analyses.

2.4.2 | Group comparisons of limbic FC

Comparisons between SCD and NC groups were carried out in each cohort separately. The standard DC of each limbic ROI was defined as a dependent variable (DV) in a generalized linear model (GLIM) implemented using the "fitglm" function in MATLAB. The sFC map of each ROI was defined as the DV in an SPM12 general linear model (GLM). All models defined group as the independent variable, controlling for age, sex, years of education, *APOE* genotype, and scanner sites (DELCODE only).

For DC analyses, significant effects were determined at $P < 0.05$ (Bonferroni-corrected). For sFC analyses, whole brain cluster-level family-wise error (FWE) correction with $P < 0.05$ (primary height threshold $P < 0.001$, cluster extent > 200 voxels) was applied.

2.4.3 | Association between limbic FC and amyloid burden

Limbic DC values or sFC maps were defined as DV in separate models for each PET subcohort. Centiloid value was defined as an independent variable, and age, sex, years of education, and *APOE* genotype as covariates. No scanner covariates were included due to small sample sizes.[59] The same statistical threshold was set as in the whole-cohort analyses.

2.4.4 | Association between limbic FC and cognition/SCD characteristics

Based on the previous whole-cohorts analyses (section 2.4.2), commonly altered FC measures across cohorts were correlated (Pearson) with cognitive performance (MMSE, AVLT, MEM), and SCD characteristics (SCD-domain, SCD-plus). Subsequently, significant behavioral variables were added as DV in a series of GLIMs within each cohort to check for group-specific effects. Model 1 estimated DV with an FC measure, with age, sex, years of education, *APOE* genotype, and scanner sites (DELCODE only) as covariates. Model 2 fitted DV with FC measure + group + FC measure × group + covariates. In the case of a significant interaction in Model 2, model 3 tested the DV with FC measure + covariates in each diagnostic group. For these exploratory analyses, $P < 0.05$, uncorrected, was considered significant.

3 | RESULTS

3.1 | Sample characteristics

Both cohorts differed slightly in sample characteristics (Table 1; Table S6 in supporting information). $DELCODE_{whole}$ showed higher age, years of education, and SCD-domain scores than $SILCODE_{whole}$, with no cohort difference in SCD-plus scores and distribution of *APOE* ε4 carriers. In $DELCODE_{whole}$, SCD subjects had slightly worse episodic memory (MEM) than NC subjects, whereas $SILCODE_{whole}$ showed no group difference in episodic memory (AVLT). $SILCODE_{whole}$ had slightly higher GDS scores than $DELCODE_{whole}$. Both cohorts presented higher GDS scores, and also higher anxiety scores (HAMA or GAI-SF) in the SCD versus NC group.

For the SCD subcohorts with amyloid-PET, $DELCODE_{PET}$ showed higher age, years of education, Centiloid values, amyloid-PET positivity rate, and SCD-domain scores than $SILCODE_{PET}$ (Table 2; Table S7 in supporting information).

3.2 | Group differences in limbic FC

For $SILCODE_{whole}$, standard DC values in the composite-limbic ROI, cingulate cortex, hippocampus, and amygdala were significantly higher in the SCD group than in the NC group (Figure 2A; Table S8 in supporting information). For $DELCODE_{whole}$, DC values in the composite-limbic ROI, hippocampus, parahippocampal cortex, and amygdala were higher in the SCD group than in the NC group (Figure 2B; Table S8 in supporting information). This was observed irrespective of the absolute threshold selected for DC calculation (Table S9 in supporting information). The standard DC scores in composite-limbic ROI, hippocampus, and amygdala were consistently increased in the SCD group across the two cohorts. They were used for the following analyses of associations between the FC measures and behavioral variables (section 3.4).

In $SILCODE_{whole}$, the SCD group showed increased sFC strength between multiple limbic ROIs (hippocampus, amygdala) and insula/putamen compared to the NC group (Figure 3A; Table S10 in supporting information). The SCD group of $DELCODE_{whole}$ exhibited increased sFC strength between the hippocampus and a cluster encompassing the right insula/putamen, amygdala, and parahippocampal cortex (Figure 3B; Table S10 in supporting information). Both cohorts showed overlapping patterns of increased connectivity between hippocampus and right insula (Figure 3C). The mean sFC values extracted from the overlapping right insula region were used to analyze associations between the FC measures and the behavioral variables in both cohorts (section 3.4).

3.3 | Association between limbic FC and amyloid load

We observed no association between standard DC scores and Centiloid values in either PET subcohort (Table S11 in supporting information).

In both subcohorts, higher Centiloid values were associated with decreased sFC strength between limbic ROIs and non-limbic areas. In $SILCODE_{PET}$, reduced connectivity was found between the cingulate cortex and the temporoparietal junction (TPJ), including the left superior temporal gyrus and supramarginal gyrus (Figure 4A; Table S12 in supporting information). In $DELCODE_{PET}$, negative associations

TABLE 1 Sample characteristics in the whole cohorts.

Characteristic	SILCODE		DELCODE		Group effect (post hoc)	Cohort effect (post hoc)	Group × cohort (post hoc)
	NC ($n = 99$)	SCD ($n = 119$)	NC ($n = 199$)	SCD ($n = 332$)			
Age	66.65 ± 4.46	66.53 ± 4.59	69.38 ± 5.49	71.16 ± 6.09	F = 3.45	F = 67.16***	F = 4.48* (b***, c***, d***)
Sex (M/F)	42 / 57	37 / 82	82 / 117	180 / 152	$\chi^2 = 8.43^{\dagger **}$	$\chi^2 = 18.76^{\S ***}$	/
Education	12.21 ± 2.91	12.66 ± 2.81	14.67 ± 2.71	14.80 ± 2.99	F = 1.53	F = 96.51***	F = 0.43
*APOE*ε4 carriers (percentage)	13.13%	27.73%	21.10%	31.93%	$\chi^2 = 7.25^{\dagger **}$ $\chi^2 = 6.92^{\ddagger **}$	–	/
SCD-domain	1.17 ± 1.07	1.87 ± 1.01	1.50 ± 1.38	2.48 ± 1.33	F = 65.54*** (e***)	F = 20.60*** (f***)	F = 1.87
SCD-plus	1.27 ± 1.01	2.97 ± .74	1.63 ± 1.49	2.61 ± 1.22	F = 183.66***	F = 0.001	F = 13.58*** (a, b***, c*, d**)
MMSE	29.04 ± 1.11	28.73 ± 1.22	29.47 ± 0.83	29.23 ± 1.00	F = 10.92** (e***)	F = 31.16*** (f***)	F = 0.23
GDS	1.79 ± 1.92	2.79 ± 2.36	0.64 ± 1.25	2.01 ± 2.06	F = 56.66*** (e***)	F = 38.37*** (f***)	F = 1.37
HAMA	2.94 ± 2.72	5.45 ± 3.90	/	/	$T = 5.39^{\ddagger ***}$	/	/
AVLT (N1-3)	21.01± 4.67	20.55 ± 3.70	/	/	T = 0.98	/	/
AVLT (N4)	7.61 ± 1.93	7.24 ± 1.94	/	/	T = 1.41	/	/
AVLT (N5)	7.35 ± 2.14	7.11 ± 1.90	/	/	T = 0.89	/	/
AVLT-reco	22.66 ± 1.53	22.30 ± 1.58	/	/	T = 1.68	/	/
GAI-SF	/	/	0.70 ± 0.84	1.17 ± 1.20	$T = 4.78^{\dagger ***}$	/	/
MEM	/	/	0.63 ± 0.45	0.39 ± 0.56	$T = 5.26^{\dagger ***}$	/	/

NOTE. Data were presented as mean ± SD.
†Comparison between NC and SCD groups within DELCODE.
‡Comparison between NC and SCD groups within SILCODE.
§Comparison of the SCD groups between SILCODE and DELCODE cohorts.
[a]Represents a significant difference between the NC and SCD groups in SILCODE.
[b]Represents a significant difference between the NC and SCD groups in DELCODE.
[c]Represents a significant difference in NC grossups between two cohorts.
[d]Represents a significant difference in SCD groups between two cohorts.
[e]Represents a significant difference between the NC and SCD groups regardless of cohorts.
[f]Represents a significant difference between the SILCODE and the DELCODE cohorts regardless of groups.
/Data were not available.
-Results were not significant.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
Abbreviations: *APOE*, apolipoprotein E; AVLT (N1-3), Auditory Verbal Learning Test: the sum of first three learning trials; AVLT (N4), Auditory Verbal Learning Test: 5 minute short-term delayed recall; AVLT (N5), Auditory Verbal Learning Test: 20 minute long-term delayed recall; AVLT-reco, Auditory Verbal Learning Test: recognition; DELCODE, DZNE Longitudinal Cognitive Impairment and Dementia; F, female; GAI-SF, Geriatric Anxiety Inventory–Short Form; GDS, Geriatric Depression Scale; HAMA, Hamilton Anxiety Rating Scale; M, male; MEM, episodic memory composition score; MMSE, Mini-Mental State Examination; NC, normal controls; SCD, subjective cognitive decline; SD, standard deviation; SILCODE, Sino Longitudinal Study on Cognitive Decline.

between amyloid burden and sFC between the composite-limbic and parahippocampal ROIs and bilateral and left cerebellum, respectively, were observed (Figure 4B; Table S12 in supporting information).

3.4 | Association between limbic FC and cognition/SCD characteristics

SCD-plus scores were significantly associated with limbic DC scores in SILCODE and with sFC between hippocampus and insula in both cohorts. No further associations were found (Table S13 in supporting information). The GLIMs for SCD-plus with additional covariates reproduced the correlation results. The models with FC × group interaction showed significant group effects for all models and almost all significant interactions except the amygdala DC of DELCODE. Further within-group analyses revealed positive effects of all FC measures on SCD-plus scores in the SILCODE NC, but not in the SCD. In DELCODE, positive effects of hippocampal DC and hippocampal-insula sFC on SCD-plus were also found in the NC group but not in the SCD group (Table S14 in supporting information).

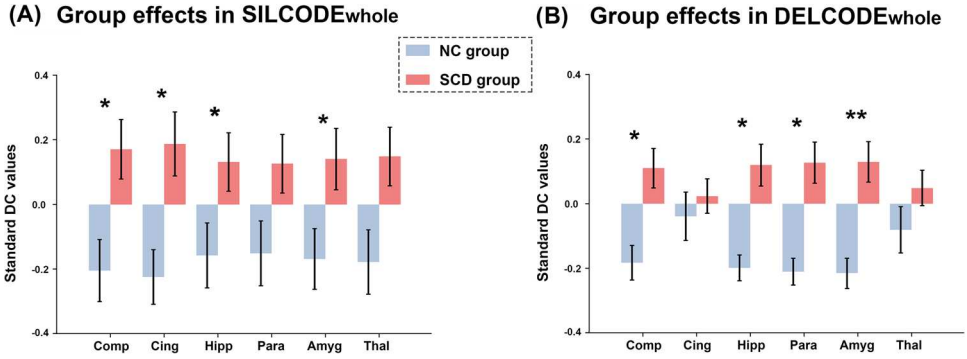

FIGURE 2 Group effects on the global limbic functional connectivity. Higher standard degree of connectivity (DC) values in the SCD group compared to the NC group in (A) $SILCODE_{whole}$ and (B) $DELCODE_{whole}$. Bonferroni-corrected, *, $P < 0.05$; **, $P < 0.01$. Amyg, amygdala; Centiloid, standardized Centiloid values representing global amyloid burden; Cing, cingulate; Comp, composite-limbic ROI; DELCODE, DZNE Longitudinal Cognitive Impairment and Dementia; Hipp, hippocampus; NC, normal controls; Para, parahippocampal cortex; ROI, region of interest; SCD, subjective cognitive decline; SILCODE, Sino Longitudinal Study on Cognitive Decline; Thal, thalamus.

4 | DISCUSSION

The current study identified consistently increased global connectivity of limbic regions across two large independent SCD cohorts from Western and Eastern populations. Furthermore, interregional connectivity between the hippocampus and right insular cortex was found to be increased in both SCD cohorts relative to their respective control groups. Results thus suggest initial adaptions in limbic FC in SCD defined by contemporary research criteria,[1,2] regardless of ethnic and cultural backgrounds. There was limited evidence that FC changes were related to amyloid burden in SCD participants with additional PET scans, leaving open whether these functional alterations are directly related to AD neuropathology. For the first time, we demonstrated that applying current SCD research definitions to Western and Eastern populations identifies overlapping functional network changes. Yet, these definitions may need further refinement to enrich preclinical AD in Chinese SCD populations and would require further research into unraveling culture-specific SCD features.

The present study made substantial efforts to align the inclusion criteria for SCD participants from two ethnic cohorts. Apart from the identical general SCD definition[1] and using the same structured questionnaire (SCD-I), both cohorts recruited SCD subjects with the key feature of concerns regarding cognitive decline. This may have contributed to our consistent cross-ethnic findings of increased limbic DC scores and hippocampus–insula connectivity in SCD. Indeed, patterns of the increased network nodal property (e.g., DC) in the hippocampus[27,28] and increased interregional connectivity between the hippocampus and insula[31] were previously reported in either Western or Eastern SCD populations. Hence, our results suggest that increased hippocampal FC in SCD should be deemed a robust finding that is valid across different ethnic and cultural backgrounds.

The insula cortex is a core region of the salience network and may be critically involved in self-awareness.[60] Hyperconnectivity between hippocampus and insula may specifically reflect increased awareness of cognitive decline in SCD.[31] In contrast, reduced connectivity of these two regions was observed in dementia patients who had become anosognosic for their memory deficits.[61] In the current study, increased hippocampus-insula connectivity consistently predicted higher SCD-plus scores in the pooled SCD and NC groups across both cohorts. Yet, post hoc analyses showed that hippocampus–insula connectivity predicted SCD-plus in NC but not SCD groups of both cohorts. Although our NC subjects did not report cognitive decline of concern, higher levels of hippocampus–insula connectivity in the presence of relatively increased SCD-plus scores (e.g., feeling cognitively worse than peers) may reflect subclinical variation in the individual awareness of cognitive deterioration. Meanwhile, the lack of complementary associations within the SCD groups may be due to ceiling effects on the SCD-plus measure. Future studies should attempt to stratify SCD subjects into different levels of self-awareness of cognition and investigate the related FC changes (e.g., using metacognition approaches[12]).

Alternatively, increased connectivity is frequently interpreted as a compensatory phenomenon,[17,53] assuming that vulnerable brain regions work harder by excessively increasing connectivity.[62] Here, one might expect positive relationships between FC increases and cognitive measures, which was not supported by the present data (Table S13 in supporting information). Moreover, explorative analyses did not show that the overlapping hippocampal–insular FC increases were linked with regional gray matter volume (and potential atrophic changes) in the hippocampus, and in the respective insular areas (Table S13 in supporting information).

This is further supported by the lack of positive associations between Centiloid values and any limbic FC measures, in either PET subcohort (Tables S11, S12 in supporting information). Accordingly, we found no direct evidence that the common FC increases were essentially driven by amyloid pathology. In the reverse direction, there were cohort-specific observations linking higher Centiloid levels to reduced sFC connectivity between the cingulate cortex and TPJ in SILCODE, and between the parahippocampal/composite-limbic ROIs and bilateral cerebellum in DELCODE. They may reflect detrimental effects of amyloid deposition in these brain networks. Similar oppositional patterns of hippocampal and parietal FC changes were previously

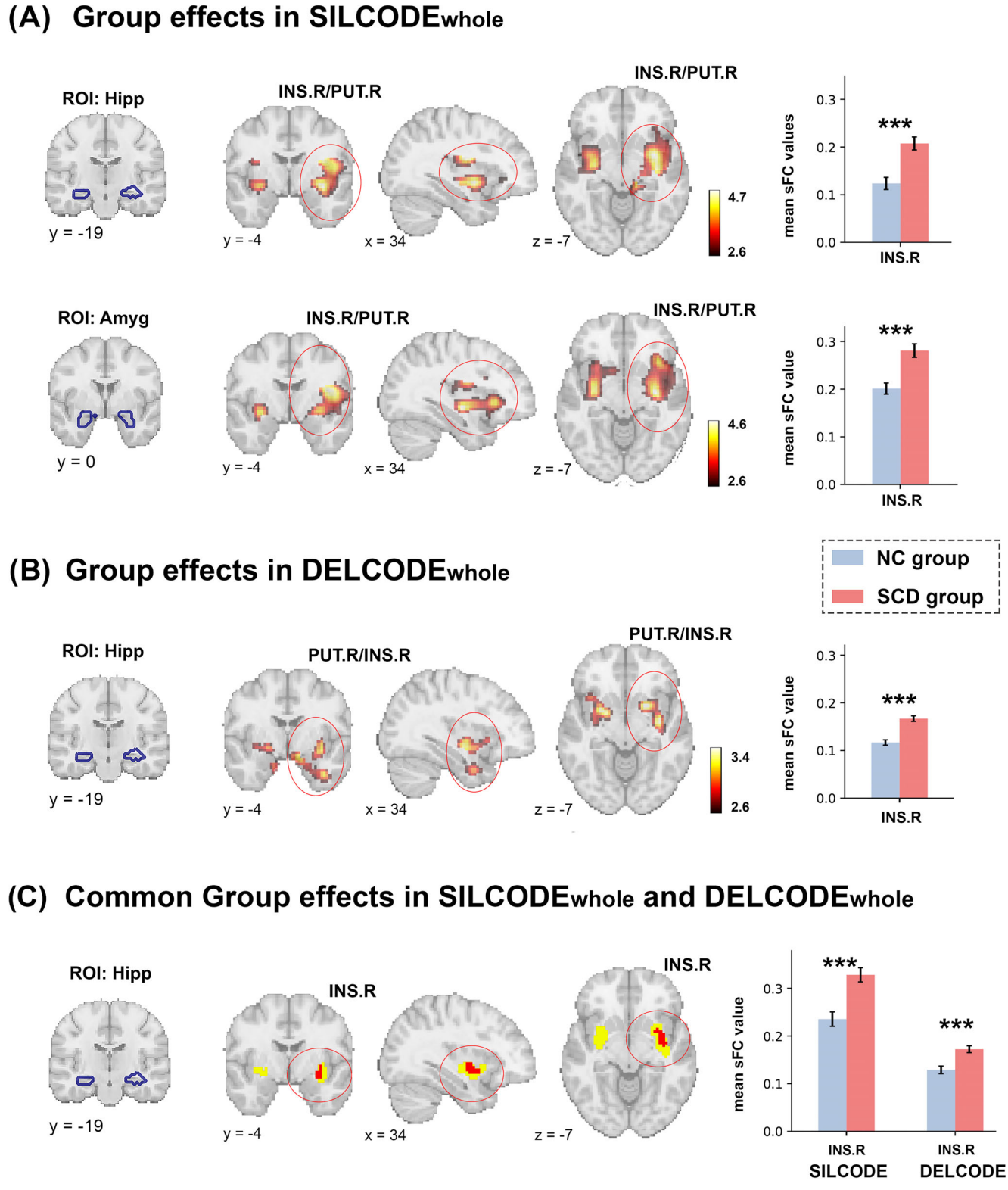

FIGURE 3 Group effects on the functional connectivity between limbic areas and other brain areas. Increased seed-based functional connectivity (sFC) between each ROI and the rest of the brain in SCD compared to NC in (A) the $SILCODE_{whole}$ cohort, and (B) the $DELCODE_{whole}$ cohort. The clusters indicated with red circles were significant at $P_{FWE} < 0.05$ (whole brain cluster-level corrected, primary height threshold $P < 0.001$, cluster extent > 200 voxels). For display purposes, the clusters in (A) and (B) were thresholded at $P_{FWE} < 0.05$ (whole brain cluster-level corrected, primary height threshold $P < 0.005$, cluster extent > 500 voxels). C, The group effects that overlapped between two cohorts; red, the overlap at the height threshold of $P < 0.001$; yellow, the overlap at the height threshold of $p < 0.005$. ***, $P < 0.001$. Amyg, amygdala; DELCODE, DZNE Longitudinal Cognitive Impairment and Dementia; FWE, family-wise error; Hipp, hippocampus; INS, insula; L, left; NC, normal controls; PUT, putamen; R, right; ROI, region of interest; SCD, subjective cognitive decline; SILCODE, Sino Longitudinal Study on Cognitive Decline.

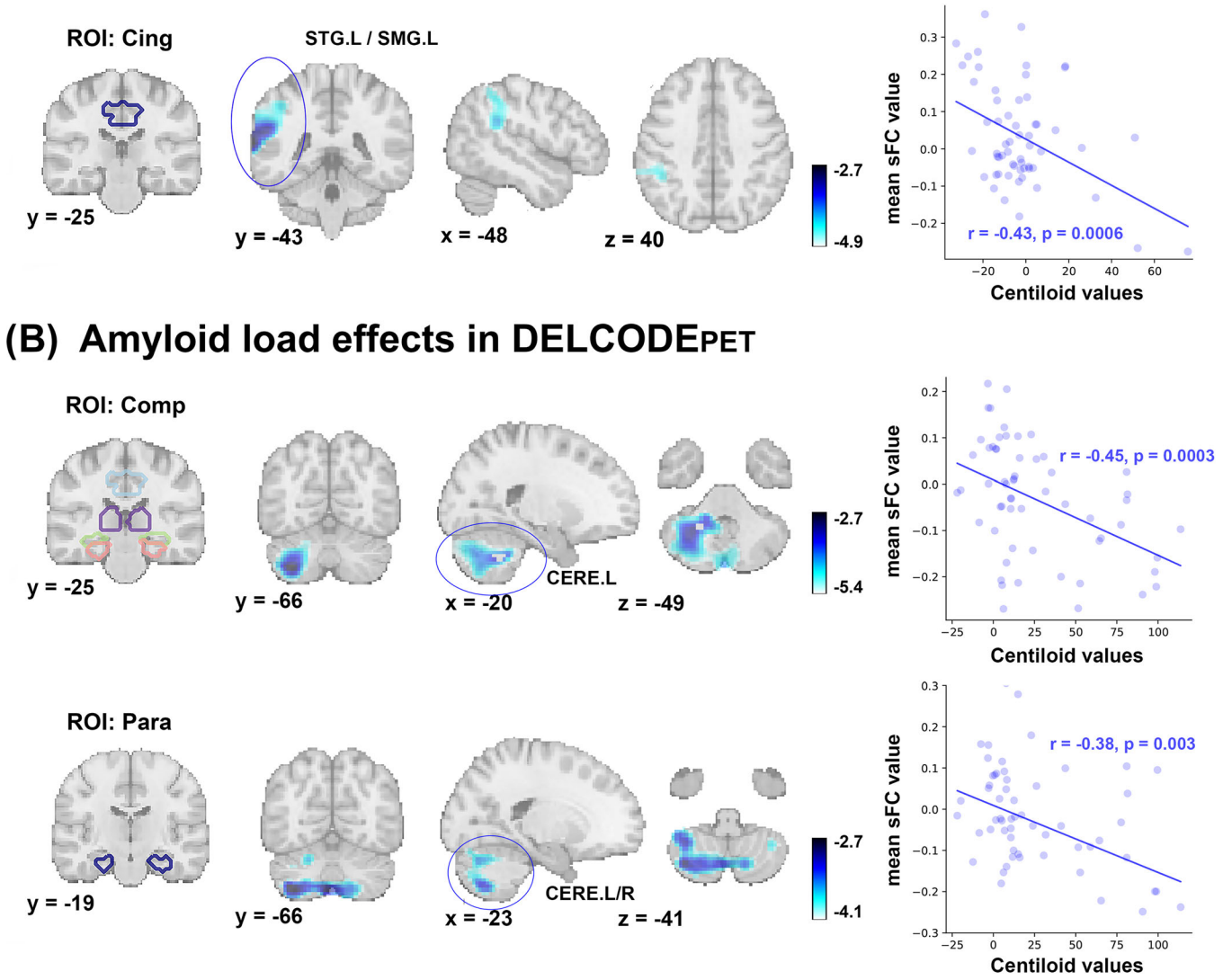

FIGURE 4 Amyloid load effects on the seed-based functional connectivity (sFC). Negative associations between Centiloid values and mean sFC values in (A) $SILCODE_{PET}$ and (B) $DELCODE_{PET}$. All clusters were significant at $P_{FWE} < 0.05$ (whole brain cluster-level corrected, primary height threshold $P < 0.001$, cluster extent > 200 voxels). For display purposes, the clusters were thresholded at $P_{FWE} < 0.05$ (whole brain cluster-level corrected, primary height threshold $P < 0.005$, cluster extent > 500 voxels). Centiloid, standardized Centiloid values representing global amyloid burden; CERE, cerebellum; Cing, cingulate cortex; Comp, composite-limbic ROI; DELCODE, DZNE Longitudinal Cognitive Impairment and Dementia; FWE, family-wise error; L, left; Para, parahippocampal cortex; R, right; ROI, region of interest; SMG, supramarginal gyrus; SILCODE, Sino Longitudinal Study on Cognitive Decline; STG, superior temporal gyrus.

observed in SCD,[27] indicating that both up- and downregulation of brain networks may already occur in SCD. The present Centiloid associations should be interpreted with caution: Amyloid-PET was only available for some SCD participants, and a restricted number of cases met conventional amyloid positivity cut-offs, especially in SILCODE. Although not representative of the whole sample, this might suggest a more heterogeneous etiology in the Chinese compared to the German SCD cohort. This may be partially explained by age differences between the PET subcohorts, given general age-related increases in amyloid positivity rates.[63] It would also concur with recent observations of lower amyloid-PET positive rates in Asian versus White Americans with cognitive impairments.[64] Finally, our cross-sectional data allow no directional inferences (i.e., amyloid burden driving FC, or vice versa[16]).

There were additional cohort-specific findings, for example, sFC group comparisons, which revealed increased amygdala–insula connectivity in SCD versus NC in SILCODE, but not DELCODE. Generally, cohort-specific results could be related to ethnic diversity in functional connectomics per se[38] and disease-induced adaptations, respectively.

While restricting analyses to participants ≥60 years,[1] SILCODE subjects were still younger than DELCODE on average, which may be influenced by general cultural differences, such as a lack of health literacy regarding neurodegenerative diseases[65] and a higher acceptance of cognitive decline[6,66] in China. Examining the main effects of the

TABLE 2 Sample characteristics in the SCD subcohorts with amyloid PET imaging.

Characteristic	$SILCODE_{PET}$ ($n = 59$)	$DELCODE_{PET}$ ($n = 59$)	Comparison
Age	66.29 ± 4.56	71.76 ± 6.06	T = 5.55 ***
Sex (M/F)	16 / 43	21 / 38	$\chi^2 = 0.98$
Education	12.54 ± 2.74	15.53 ± 3.03	T = 5.60 ***
APOEε4 carriers (percentage)	30.51%	38.98%	$\chi^2 = 0.93$
Centiloid	−3.27 ± 18.80	25.60 ± 34.01	T = 5.71***
Aβ+ (percentage)	8.47 %	37.29%	$\chi^2 = 13.88$***
SCD domains	1.98 ± 1.04	2.73 ± 1.05	T = 3.88***
SCD plus	2.93 ± 0.76	2.92 ± 0.86	T = 0.11
MMSE	29.07 ± 1.23	29.25 ± 1.12	T = 0.86
GDS	2.46 ± 2.06	2.01 ± 1.89	T = 1.26
HAMA	4.86 ± 3.85	/	/
AVLT (N1-3)	21.61 ± 3.62	/	/
AVLT (N4)	7.66 ± 2.03	/	/
AVLT (N5)	7.68 ± 2.11	/	/
AVLT-reco	22.33 ± 1.03	/	/
GAI-SF	/	1.05 ± 1.02	/
MEM	/	.43 ± 0.59	/

NOTE: Data were presented as mean ± SD.
/Data were not available.
***$P < 0.001$.
Abbreviations: Aβ+: Rate of amyloid-positive cases with Centiloid ≥ 20;[59] *APOE*, apolipoprotein E; AVLT (N1-3), Auditory Verbal Learning Test: the sum of first three learning trials; AVLT (N4), Auditory Verbal Learning Test: 5 minute short-term delayed recall; AVLT (N5), Auditory Verbal Learning Test: 20 minute long-term delayed recall; AVLT-reco, Auditory Verbal Learning Test: recognition; Centiloid, standardized Centiloid values representing global amyloid burden according to Klunk et al.[58] DELCODE, DZNE Longitudinal Cognitive Impairment and Dementia; F, female; GAI-SF, Geriatric Anxiety Inventory–Short Form; GDS, Geriatric Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; M, male; MEM, memory assessment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SCD, subjective cognitive decline; SD, standard deviation; SILCODE, Sino Longitudinal Study on Cognitive Decline.

age covariates in our statistical models, we found no overlap with our primary findings (Tables S15-S18 in supporting information). Therefore, age differences between cohorts are unlikely to affect the main findings.

While DELCODE only included memory clinic SCD patients, SILCODE partially recruited via advertisements, reflecting fundamental differences in primary health care (see supporting information): German family practice–based primary care is currently not affordable in China, making medical service via internet a critical complementary approach.[67] We also performed secondary analyses using the memory clinic SCD subgroup in SILCODE, which confirmed our main findings (see Table S19 in supporting information), suggesting that the source of SCD recruitment did not impact the current results, although this needs to be tested explicitly in future studies.

For the first time, we demonstrated overlapping functional brain network changes in both Eastern and Western populations when applying the current SCD research definition. Yet, this definition may not achieve the same level of enrichment of preclinical AD in the Chinese SCD population as in the German SCD population, although such inferences are preliminary due to the small sample size of SCD individuals with amyloid-PET. Our findings regarding commonly increased global limbic connectivity and hippocampus–insula connectivity in SCD may reflect a heightened awareness of cognitive decline, irrespective of underlying AD pathology. Future studies need to investigate the possible underlying cause of Chinese SCD, such as neuropsychiatric symptoms, vascular disease, or social factors, and to identify culturally specific features[64] to achieve enrichment of preclinical AD and guide future treatment and prevention.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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