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ORIGINAL COMMUNICATION

Olfactory identification impairment in cerebral small-vessel disease indicates cognitive network disconnection and predicts accelerated cognitive decline

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Abstract

Background Olfactory identification impairment is a well-established early screening index for cognitive decline in neurodegenerative disorders. However, whether this simple sensory test can similarly detect or predict cognitive deficits in cerebral small vessel disease (CSVD)—a leading cause of vascular cognitive impairment—remains unclear.

Methods All participants—including 193 CSVD patients and 164 normal controls (NC)—completed the University of Pennsylvania Smell Identification Test (UPSIT) and a comprehensive neuropsychological battery. Multimodal MRI analyses were conducted to identify structural and functional abnormalities associated with UPSIT performance. A cognitive follow-up assessment was performed 24 months post-baseline, and the rate of cognitive decline was annualized.

Results Compared to NC, CSVD patients exhibited significantly lower UPSIT scores ($p < 0.001$). UPSIT performance correlated strongly with cognition. Local structural and functional abnormalities in primary and secondary olfactory cortices did not reliably predict UPSIT performance in CSVD patients. In contrast, dorsolateral prefrontal cortex functional connectivity strength was significantly associated with odor-identification performance. Mediation models further demonstrated that greater white matter lesion burden indirectly impaired olfactory identification via disrupted inter-network connectivity between the salience network (SN) and posterior default mode network (pDMN). CSVD patients with baseline UPSIT < 20 exhibited a steeper annual MMSE decline than those with UPSIT ≥ 20 (1.0 vs. 0.5 points per year; $p < 0.001$).

Conclusion Olfactory identification impairment in patients with CSVD reflects disruption of higher-order cognitive networks, and a baseline UPSIT score below 20 predicts accelerated cognitive decline.

Keywords Olfactory identification · Functional connectivity · Cognitive function · Cerebral small vessel disease

Introduction

Olfactory identification is a complex neural cascade integrating and depending on the functions of olfactory receptors, the olfactory nerve, and the olfactory cortex[1]. In Alzheimer's disease (AD), olfactory dysfunction (OD) is an early noncognitive indicator that often precedes memory decline by several years, reflecting pathological protein aggregation in vulnerable regions—such as the entorhinal cortex—and progressive disruption of higher-order cognitive networks[2–4]. Similarly, in Parkinson's disease (PD), OD is one of the earliest non-motor features. OD may be related to Lewy bodies composed of misfolded α-synuclein in the olfactory bulb (OB) and propagating via olfactory tracts into frontostriatal circuits, often preceding motor symptom onset by several years and potentially predicting progression from prodromal to manifest PD[5–7]. These findings underscore that OD not only reflects disruptions in structural and functional integrity and captures prodromal neurodegenerative processes, but also provides a sensitive window for early disease recognition and prevention[8].

Cerebral small vessel disease (CSVD) is characterized by diffuse white-matter hyperintensities (WMHs), lacunar infarcts, cerebral microbleeds, and enlarged perivascular

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spaces, and is a major contributor to vascular cognitive impairment in older adults [9]. Prior studies in patients with metabolic syndrome (MetS)—a cluster of largely asymptomatic vascular risk factors—have also demonstrated a significant association between white matter alterations and cognitive impairment[10]. Despite this burden, rapid and affordable biomarkers to identify CSVD patients at the highest risk for cognitive decline remain lacking. Recent studies demonstrate that successful odor identification also requires engagement of neocortical regions [11–13]. Du et al. reported that, among dementia-free older adults, anosmia is significantly associated with increased white matter hyperintensity (WMH) burden, thereby linking olfactory impairment to cerebral microvascular pathology [14]. Olfactory identification—a brief, non-invasive sensory test—has proven sensitive to early cognitive changes in neurodegenerative disorders; however, its value in CSVD remains unexplored.

In this study, we evaluated the relationship between olfactory identification performance and neuropsychological profiles in patients with CSVD, as well as the underlying structural and functional mechanisms, to determine whether olfactory testing can serve as a reliable indicator of cognitive and brain impairment and thereby facilitate earlier diagnosis and timely intervention.

Methods

Participants

We consecutively recruited 431 participants—including patients, caregivers, and volunteers—from the Clinic at the First Hospital of Jilin University. After applying inclusion and exclusion criteria, 357 participants were enrolled: 193 CSVD patients and 164 normal controls (NC). Written informed consent was obtained from all participants and their caregivers or informants. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University, ensuring full compliance with established ethical guidelines.

CSVD was diagnosed using established neuroimaging criteria, defined by the presence of at least one of the following: recent small subcortical infarcts, presumed vascular lacunes, white matter hyperintensities, enlarged perivascular spaces, cerebral microbleeds, cortical superficial siderosis, brain atrophy, or cortical microinfarcts. Patients with acute ischemic stroke or transient ischemic attack (TIA) at enrollment were excluded. At baseline, CSVD-related clinical manifestations were recorded. A subset of patients had a history of lacunar syndrome (LS; $n = 28$, 14.51%) and were further classified into canonical subtypes: pure motor hemiparesis (PMH; $n = 12$, 6.21%), pure sensory stroke (PSS; $n = 11$, 5.69%), sensorimotor stroke (SMS; $n = 1$, 0.52%), ataxic hemiparesis (AH; $n = 1$, 0.52%), dysarthria–clumsy hand syndrome (DCH; $n = 2$, 1.04%), and atypical lacunar syndromes ($n = 1$, 0.52%). For these patients, eligibility required a stroke onset at least 6 months before enrollment to minimize acute-phase effects on outcome assessment. The remaining participants had no history of acute stroke or TIA and presented exclusively with chronic CSVD phenotypes ($n = 165$, 85.49%), defined as either (i) fulfilling neuroimaging criteria without overt clinical symptoms or (ii) exhibiting cognitive impairment, gait or other motor disturbances, and urinary dysfunction, alone or in combination. These phenotypic categories were not mutually exclusive, as most patients with a history of LS also exhibited chronic CSVD phenotypes.

Control participants met the following inclusion criteria: (1) informant-confirmed normal cognitive function; (2) Mini–Mental State Examination (MMSE) score ≥ 26; (3) Clinical Dementia Rating (CDR) score of 0.

The CSVD non-dementia subgroup met the following inclusion criterion: MMSE ≥ 26 at baseline. Participants in the full cohort and in the CSVD non-dementia subgroup were stratified by educational attainment at the cohort-wide median (12 years) into education-matched subgroups (lower education, < 12 years; higher education, ≥ 12 years).

Exclusion criteria were: (1) Hamilton Depression (HAMD) or Hamilton Anxiety (HAMA) Rating Scale score ≥ 7; (2) history of head trauma, poisoning, substance abuse, metabolic brain injury, or other disorders causing cognitive impairment (e.g., Alzheimer's disease, Parkinson's disease, syphilis); (3) inability to complete neuropsychological assessments or contraindications to MRI; (4) history of upper respiratory infections, allergic rhinitis, nasal pathology (e.g., mass lesions), chronic sinusitis, or craniofacial trauma.

Two neurologists, each with 12–15 years of experience, independently established clinical diagnoses; discrepancies were resolved through consensus meetings. Figure 1. shows a flowchart of participant grouping.

Assessment of neuropsychological and olfactory identification functions

A standardized battery of neuropsychological tests was administered to all participants. Cognitive performance and daily functioning were assessed using the Mini–Mental State Examination (MMSE), Vascular Dementia Assessment Scale–Cognitive subscale (VADAS-Cog), Clinical Dementia Rating (CDR), Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), and the Neuropsychiatric Inventory (NPI). Anxiety and depression were evaluated using the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA),

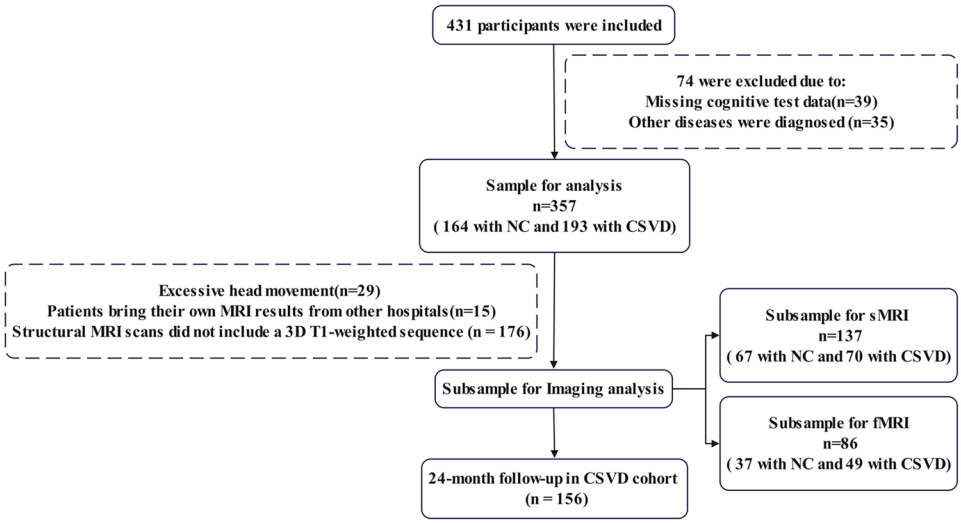

Fig. 1 Flowchart depicting the grouping of study participants

respectively. For participants undergoing fMRI, memory and executive functions were assessed using the Auditory Verbal Learning Test (AVLT) and completion times on the Symbol Trail Test A (STT-A) and B (STT-B).

All participants completed the University of Pennsylvania Smell Identification Test (UPSIT)[15]. The test booklet contains 40 pages, each featuring a microencapsulated odorant and a forced-choice question with four response options. For each odor, participants scratched the page to release the scent and selected the most appropriate option. Each correct identification scored one point; incorrect or omitted responses scored zero. Each participant's olfactory performance was quantified by the UPSIT score, which ranges from 0 to 40.

At the 24-month follow-up, participants who experienced an acute stroke or were lost to follow-up were excluded, resulting in 156 individuals who completed a repeat MMSE. Annualized cognitive decline was calculated by dividing the change in MMSE score between baseline and month 24 by the precise follow-up duration (in years). For group comparisons, participants were stratified into lower- and higher-performance subgroups based on a median UPSIT score of 20.

MRI data acquisition and analysis

MRI acquisition

All participants were scanned on a Philips Ingenia 3.0 T MRI system (Philips Healthcare) in the Radiology Department of the First Hospital of Jilin University. Each participant completed the following imaging sequences: three-dimensional T1-weighted imaging (3D-T1WI), resting-state functional MRI (rs-fMRI), T2-weighted imaging (T2WI), and T2-FLAIR.

A high-resolution 3D-T1WI dataset was acquired for tissue segmentation, spatial registration, and volumetric analysis using the following parameters: voxel size 1 mm × 1 mm × 1 mm; echo time (TE) 3.3 ms; repetition time (TR) 7.2 ms; slice thickness 1 mm (no gap); field of view (FOV) 256 mm × 256 mm; flip angle 7°.

Participants were asked to rest with eyes closed during the echo-planar imaging used for rs-fMRI. This sequence employed: voxel size 3.5 mm × 3.5 mm × 4.2 mm; echo time (TE) 30 ms; repetition time (TR) 2000 ms; field of view (FOV) 64 mm × 64 mm; flip angle 90°.

Assessment of CSVD burden score

White-matter lesion burden was quantified on T2-FLAIR images using the Age-Related White Matter Changes (ARWMC) scale. Leukoaraiosis in five regions per hemisphere (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial) was rated 0–3 (0 = no lesions; 3 = confluent lesions), and the regional scores were summed to generate a total ARWMC score (0–30)[16].

3D-T1WI image analysis

The Computational Anatomy Toolbox version 12 (CAT12) was employed to preprocess 3D-T1WI imaging data. Preprocessing comprised four sequential steps. First, head motion correction was applied to T1-weighted images. Second, spatial segmentation via voxel-based morphometry (VBM) partitioned each scan into gray matter volume (GMV), white matter volume (WMV), cerebrospinal fluid, and total intracranial volume (TIV). Third, images were normalized to a standard template to reduce intersubject variability. Fourth, all data were smoothed using a Gaussian kernel with a 6 mm full width at half maximum (FWHM).

Using CAT12, the volumes of key brain structures were automatically calculated according to the Automated Anatomical Labeling (AAL) atlas. Notably, the entorhinal cortex is not defined as a separate region in the AAL atlas; its voxels are subsumed within the parahippocampal gyrus[17, 18].

rs-fMRI analysis

Resting-state fMRI (rs-fMRI) data were preprocessed using the DPARSF software package[19] with the following pipeline: (1) Removed the first 10 time points from each participant's functional series. (2) Performed slice-timing correction. (3) Realigned all volumes to a reference image using rigid-body registration and excluded scans with translation > 3 mm or rotation > 3°. (4) Spatially normalized images to Montreal Neurological Institute (MNI) space with isotropic voxels of $3 \times 3 \times 3$ mm^3. (5) Detrending and regression. (6) Defined fractional amplitude of low-frequency fluctuation (fALFF) as the ratio of summed amplitudes within the 0.01–0.08 Hz band to summed amplitudes across all detectable frequencies. Applied a temporal band-pass filter (0.01–0.08 Hz) to remove high-frequency noise and low-frequency drift. Smoothed voxel-wise fALFF maps and converted them to z-scores for subsequent statistical analysis. (7) Smoothing, using a Gaussian kernel with a 6 mm full width at half maximum (FWHM).

Regional homogeneity (ReHo) was computed voxel-wise using Kendall's coefficient of concordance (KCC) across each voxel and its 26 nearest neighbors (cluster size = 27). This measure quantifies the synchronization of local spontaneous activity. The resulting ReHo maps were normalized to z-scores by subtracting the global mean KCC value and dividing by the global standard deviation prior to group-level analysis.

Independent component analysis (ICA) was conducted using the GIFT toolbox (version 3.0)[20] to decompose each participant's preprocessed data into independent components (ICs). First, at both individual and group levels, the dimensionality of the preprocessed fMRI data was reduced via a two-step principal component analysis (PCA). Second, twenty-nine independent components were extracted using the Infomax algorithm. To assess component stability, the Infomax ICA was repeated 100 times with the ICASSO method, and this procedure was performed in five separate runs to select components with an average intra-cluster similarity exceeding 80%. Third, spatial components and their corresponding time series were reconstructed for all participants using multiple linear regression. Finally, resting-state networks (RSNs) were identified by visual inspection, ensuring that primary RSNs were localized within gray matter. Ten RSNs were manually identified and selected for further analysis. These comprised the anterior and posterior default mode networks (aDMN, pDMN), left and right frontoparietal networks (LFPN, RFPN), salience network (SN), dorsal attention network (DAN), sensorimotor network (SMN), medial and lateral visual networks (mVN, lVN), and auditory network (AN).

This study examines voxel-wise functional connectivity strength (FCS) within predefined regions of interest (ROIs). FCS is defined as the voxel-wise Weighted degree centrality, quantifying the sum of functional connections between each voxel and all other brain voxels. Specifically, mean FCS values within each ROI were extracted before normalizing the FCS images. The FCS threshold was set to 0.6, based on previous studies demonstrating that this cutoff effectively eliminates spurious connectivity values and noise.

Statistical analyses

Statistical analyses were performed in SPSS version 24.0. Demographic and clinical variables were compared using independent-samples *t*-tests or χ^2 tests for normally distributed data and Mann–Whitney U tests for non-normally distributed variables. Associations between UPSIT scores and cognitive or imaging measures were first assessed by univariate linear regression. Variables with $p < 0.05$ were subsequently entered into multivariate Linear regression models adjusted for age, sex, and years of education. To examine causal pathways, mediation analyses were conducted using the PROCESS macro with 5000 bootstrap resamples to estimate bias-corrected 95% confidence intervals for indirect effects.

For MRI data, voxel-wise comparisons and regression analyses were performed in SPM12. A stringent voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ (Gaussian Random Field–corrected) were applied. Significant clusters were anatomically labeled using the AAL atlas.

Results

Demographic, clinical, and neuropsychological characteristics

As shown in Table 1, there were no significant differences between the CSVD and NC groups in age, sex distribution, anxiety scores, depression scores, or neuropsychiatric symptom severity (all $p > 0.05$). Education level was significantly lower in the CSVD group compared to controls ($p < 0.001$). Global cognitive performance, assessed by the MMSE, CDR, and VADAS-Cog, was significantly poorer in the CSVD group ($p < 0.001$). Similarly, activities of daily living scores were significantly lower in CSVD patients than in NC participants ($p < 0.001$). Olfactory identification ability, measured by the UPSIT, was reduced in the CSVD cohort compared to NC participants ($p < 0.001$), supporting

Table 1 Demographic information overall participants

	NC $n=164$	CSVD $n=193$	*P* value
Age, years	63(58–69)	65(61–69)	0.150
Gender, female	58(35.37%)	83(43%)	0.141
Education	15(12–15)	9(9–12)	<0.001***
MMSE	29(28–29.75)	24(21–26)	<0.001***
VADAS-Cog	6(5–7)	21(16–28)	<0.001***
HAMD	3(1–4)	2(1–4)	0.082
HAMA	2(1–3.75)	2(1–3)	0.090
ADCS-ADL	76(75–77)	66(57–72)	<0.001***
CDR	0(0–0)	1(0.5–1)	<0.001***
NPI	0(0–0)	0(0–1)	0.565
UPSIT	26(23.25–28)	20(17–22)	<0.001***
ARWMC Score	1(1–2)	9(8–11)	<0.001***
Smoking history	55(33.54%)	71(36.79%)	0.522
Hypercholesterolemia	24(14.63%)	41(21.24%)	0.107
Hypertension	67(40.85%)	74(38.34%)	0.629
Diabetes mellitus	26(15.85%)	34(17.62%)	0.657
Alcohol use history	63(38.41%)	70(36.27%)	0.676

Symbols'***','**'and'*'represent the significance level, $p<0.001$, $p<0.01$ and $p<0.05$, CI, confidence interval, respectively

NC Normal control, *CSVD* Cerebral small vessel disease

evidence that patients with CSVD exhibit pronounced olfactory identification deficits. Finally, ARWMC score were significantly higher in the CSVD group than in normal controls ($p<0.001$), indicating impaired white matter integrity.

In CSVD non-dementia and education-matched subgroup analyses, UPSIT scores were also significantly lower than those in normal controls (Fig. S1, Table S1).

Association between cognitive function and olfactory identification

In univariate linear regression, UPSIT scores were strongly positively associated with global cognition, as measured by the MMSE ($\beta=0.535$, 95% CI 0.445–0.625; $p<0.001$). Higher UPSIT performance also corresponded to lower VADAS-Cog total scores ($\beta=-0.936$, 95% CI −1.175–0.697; $p<0.001$) and to higher ADL ($\beta=0.854$, 95% CI 0.558–1.150; $p<0.001$) (Fig. 2A, B, D). Beyond global measures, UPSIT performance showed significant correlations with memory (AVLT total and subdomain scores; Fig. 2F–G) and with executive function (Shape Trial Test A and B completion times; Fig. 2C). Subscale analysis of the VADAS-Cog (Fig. 2E) revealed that olfactory identification was associated with short- and long-term memory subdomains and with the executive subscale, but showed no association with language components.

In multivariable models adjusted for age, sex, years of education and past medical history (Table S2), all associations remained significant. These results demonstrate that, in CSVD patients, olfactory identification ability is closely associated with—and evolves in parallel with—declines in global cognition, executive function, and memory.

Within the CSVD non-dementia subgroup, lower UPSIT scores were also significantly associated with worse global cognition on VADAS-cog and poorer ADL performance, whereas the association with MMSE was not significant (Table S3).

Structural and functional correlates of olfactory pathway regions and olfactory identification

Voxel-based morphometry and resting-state analyses revealed gray matter atrophy, reduced ReHo, and diminished fALFF in olfactory pathway regions in CSVD patients compared with controls (Fig. 3A, C, E; Table S4–S6). However, in multivariable linear regressions adjusted for confounding factors, regional gray matter volume (Fig. 3B), fALFF (Fig. 3F) in primary and secondary olfactory regions did not predict UPSIT performance in the CSVD cohort (all $p>0.05$). Similarly, aside from the parahippocampal gyrus (Fig. 3D), ReHo in all other olfactory pathway regions did not correlate with odor-identification scores.

This dissociation suggests that olfactory-identification decline in CSVD is not primarily attributable to focal atrophy or primary functional disruption within the olfactory pathway.

Influence of network functional connectivity on olfactory identification performance

In CSVD patients, inter-network functional connectivity was significantly altered compared to controls ($p<0.05$). Alterations were most pronounced in the LFPN, pDMN, and SN. Both the negative inter-network functional connectivity between the salience network SN and pDMN and the positive inter-network connectivity between SN and RFPN are reduced. (Fig. 4A, B). Intra-network analyses revealed focal decreases in functional connectivity within key hubs of the pDMN, FPN, SN, and DAN—specifically the dorsolateral prefrontal cortex (dlPFC), precuneus, angular gyrus, insula, and superior parietal lobule (Fig. 4C; Table S7).

We performed multivariable linear regressions—adjusted for age, sex, and education—on regions with altered inter-network connectivity to determine whether these metrics predict UPSIT performance. Inter-network connectivity between the SN and pDMN significantly predicted UPSIT scores. Subsequent mediation analysis—adjusted for the same covariates—revealed that white matter lesion burden indirectly influences olfactory identification and memory

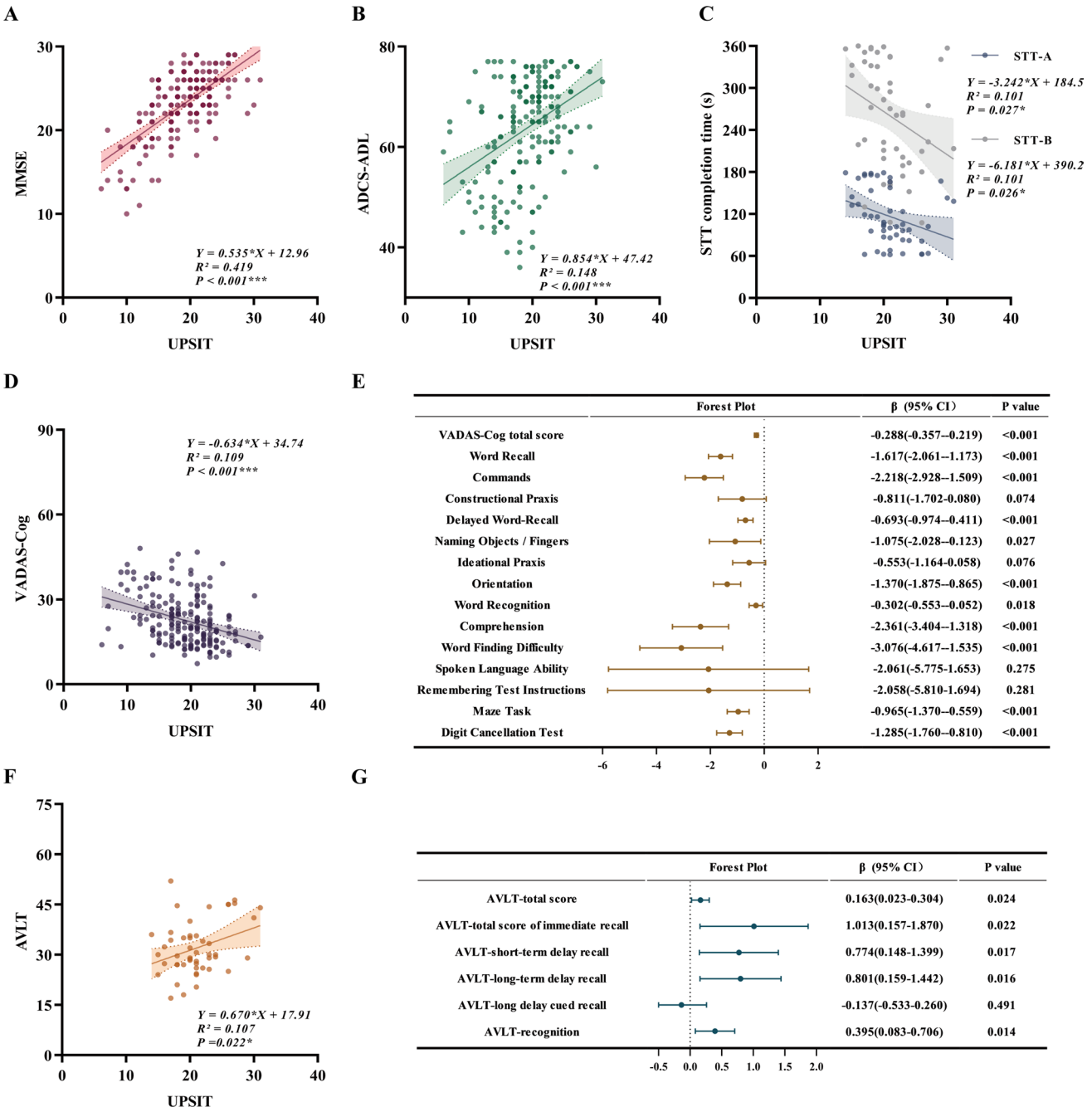

Fig. 2 Linear associations between olfactory identification and cognitive measures. **A** MMSE; **B** ADCS-ADL; **C** STT-A and B completion times; **D** VADAS-Cog total score; **E** Multivariable linear regression of UPSIT scores versus VADAS-Cog total and domain scores; **F** AVLT total score; **G** Multivariable linear regression of UPSIT scores versus AVLT total and domain scores. Standardized β coefficients (95% confidence intervals) and p-values are presented for each model, adjusted for age, sex, and education

function via altered SN–pDMN connectivity (Fig. 4D), consistent with network-based cognitive reserve models.

Additionally, we quantified the integrative capacity—or"hubness"—of regions exhibiting intra-network disruptions by extracting their FCS. Linear regression analyses showed that higher FCS of the dlPFC was significantly associated with better olfactory identification and with more efficient executive function, as evidenced by faster completion times on STT-A and STT-B (all $p < 0.05$) (Fig. 4E; Table S8).

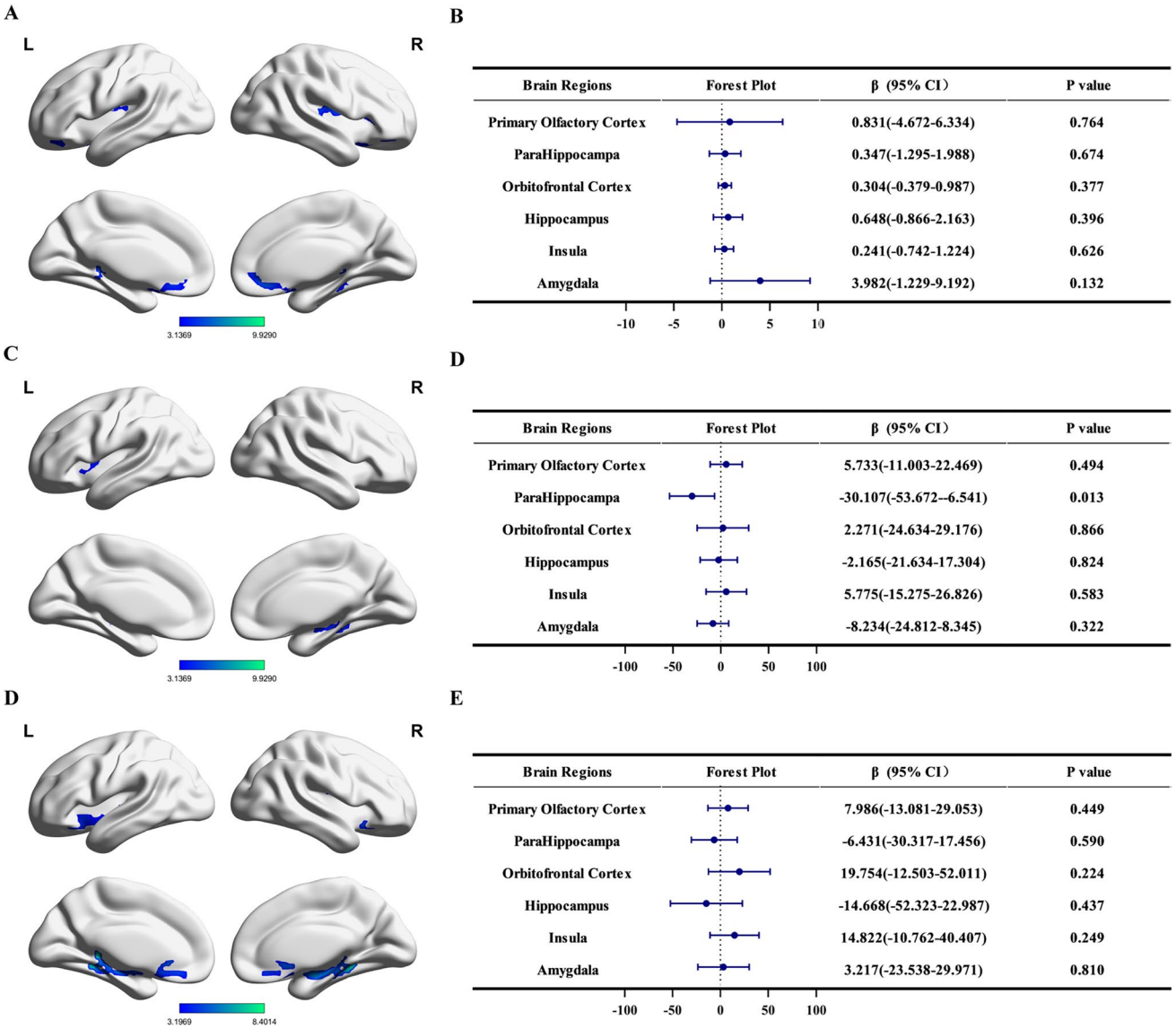

Fig. 3 Structural and functional alterations in olfactory pathway regions and their associations with olfactory identification. **A** Voxel-wise comparison of gray matter volume in olfactory pathway regions between CSVD patients and NC, with voxel-level $p < 0.001$ and cluster-level $p < 0.05$ (Gaussian Random Field (GRF)–corrected). **B** Multivariable linear regression of UPSIT scores versus regional gray matter volume, adjusted for age, sex, education, and total intracranial volume (TIV); standardized β coefficients (95% CI) and p-values are presented. **C** Voxel-wise comparison of regional ReHo between CSVD patients and NC, with voxel-level $p < 0.001$ and cluster-level $p < 0.05$ (GRF–corrected). **D** Multivariable linear regression of UPSIT scores versus regional ReHo, adjusted for age, sex, and education; standardized β coefficients (95% CI) and p-values are presented. **E** Voxel-wise comparison of regional fALFF between CSVD patients and NC, with voxel-level $p < 0.001$ and cluster-level $p < 0.05$ (GRF–corrected). **F** Multivariable linear regression of UPSIT scores versus regional fALFF, adjusted for age, sex, and education; standardized β coefficients (95% CI) and *p*-values are presented

Lower baseline olfactory identification performance predicts faster global cognitive decline

Using the cohort-wide median UPSIT score of 20 as the cutoff, CSVD patients with UPSIT < 20 ($n = 72$) exhibited a larger annual MMSE decline—median 1.0 point/year (95% CI 0.5–1.0)—than those with UPSIT ≥ 20 ($n = 84$), whose median decline was 0.5 point/year (95% CI 0–0.5; $p < 0.001$), supporting that baseline olfactory impairment predicts faster global cognitive decline. In CSVD non-dementia and education-matched subgroup analyses, this result remained directionally consistent and statistically significant (Figure S2).

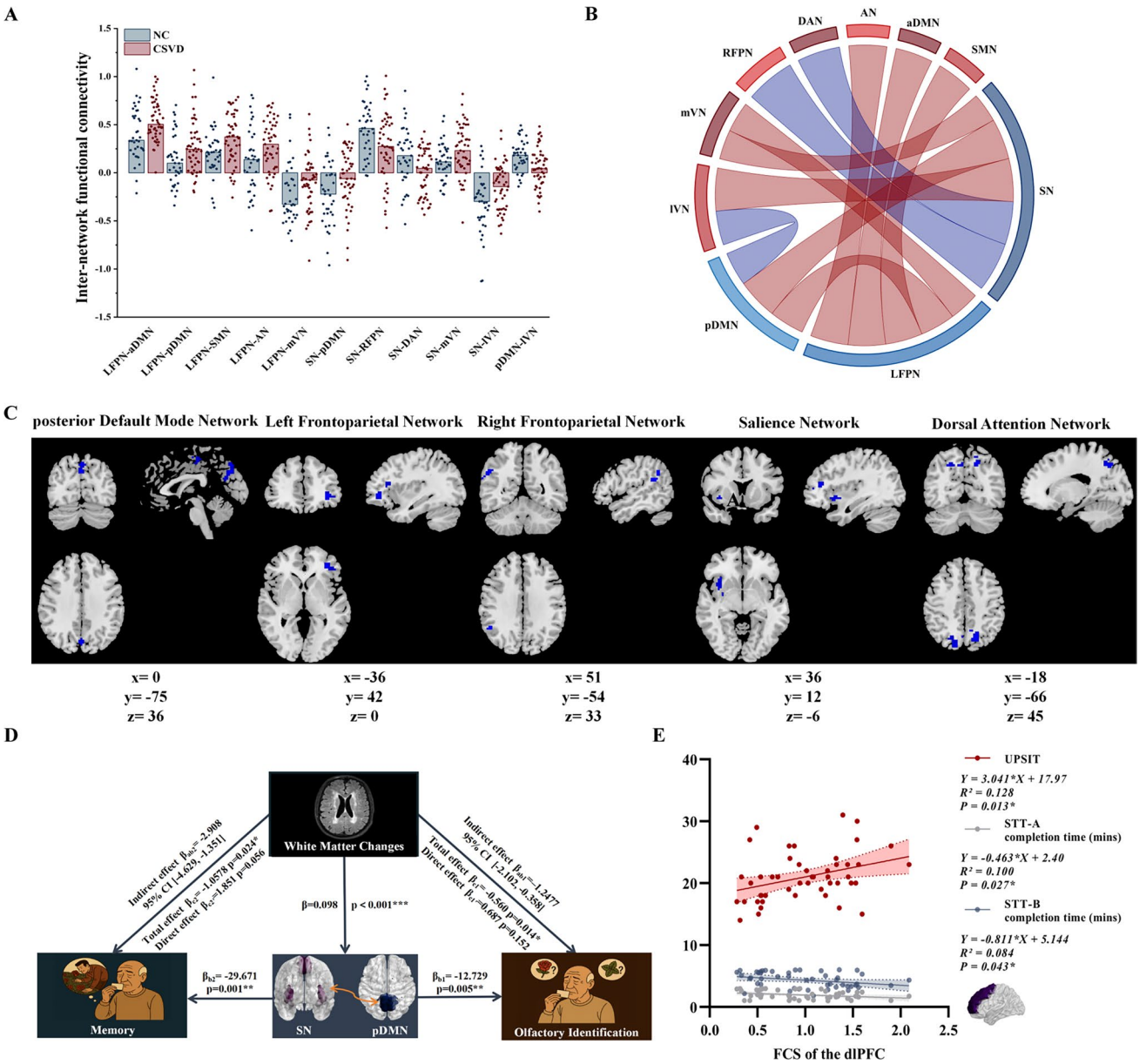

Fig. 4 Associations between inter- and intra-network functional connectivity and olfactory identification performance. **A** Compared with normal controls, the CSVD group exhibited significantly altered inter-network functional connectivity strength ($p < 0.05$). **B** Chord diagram illustrating altered inter-network connectivity: red indicates increased positive connectivity or reduced negative connectivity, and blue indicates decreased positive connectivity or enhanced negative connectivity. **C** Voxel-wise comparison of intra-network functional connectivity, highlighting clusters of significant alterations within each RSN (voxel-level $p < 0.001$; cluster-level $p < 0.05$, GRF-corrected). **D** Mediation model illustrating that in CSVD patients, white matter lesion burden indirectly influences olfactory identification (UPSIT) and memory function (AVLT) via altered inter-network connectivity between the SN and pDMN. All path estimates are adjusted for age, sex, and education. **E** Linear associations were examined between dorsolateral prefrontal cortex(dlPFC) FCS and both olfactory identification performance (UPSIT) and executive function (STT completion times)

Discussion

In this study, we show that olfactory identification deficits—previously validated as a cognitive-decline screening index in neurodegenerative disorders—also occur in CSVD and reflect higher-order network disintegration rather than primary olfactory-pathway damage. The marked association between olfactory identification and cognitive performance Likely arises from their shared reliance on memory and executive circuits. A baseline UPSIT score below 20 predicts accelerated cognitive decline in CSVD.

Demographic and neuropsychological comparisons confirmed that CSVD patients have significantly poorer global cognition, executive function, and memory performance, as well as reduced activities of daily living, compared to matched controls. These findings corroborate previous reports that CSVD patients exhibit diffuse cognitive decline across multiple cognitive domains[21, 22]. Within the CSVD non-dementia subgroup, UPSIT scores were significantly lower than those in normal controls, providing preliminary evidence that olfactory impairment may precede overt dementia in CSVD. Regression analyses showed that olfactory identification correlates strongly with global cognitive status, daily functioning, and, in particular, with memory and executive function. We propose two non–mutually exclusive mechanisms explaining the link between olfactory identification and cognitive performance in CSVD. First, olfactory identification relies on higher-order cognitive processes: successful odor labeling requires accurate mnemonic retrieval of stored odor representations and engages executive functions—such as cognitive flexibility, response selection, and inhibition of competing candidates—to select the correct response[23–25]. Impairments in these domains directly reduce UPSIT performance. Second, olfactory and cognitive functions share overlapping association cortices; damage to these shared hubs in CSVD leads to parallel declines in odor identification and global cognitive abilities [26, 27]. Olfactory identification deficits in CSVD patients may reflect broader cognitive dysfunction and afford clinicians a window to implement optimal blood-pressure targets and other vascular-risk interventions earlier, potentially delaying disease progression and preserving cognitive function.

Prior neurodegenerative research indicates that olfactory impairment frequently corresponds to focal accumulation of pathological proteins in olfactory pathways[28, 29]. In Parkinson's disease, α-synuclein aggregates initially emerge in the olfactory bulb and then spread via the anterior olfactory nucleus and brainstem to broader cortical areas, correlating with early hyposmia and later motor and cognitive decline[30, 31]. Similarly, in preclinical Alzheimer's disease, Braak stage I features neurofibrillary tangle deposition in the entorhinal cortex, causing structural atrophy and functional hypoactivity in primary and secondary olfactory cortices, thereby driving odor-identification deficits[4, 32, 33].

Motivated by these parallels, we used multimodal MRI to determine whether similar focal damage underlies hyposmia in CSVD. As expected, CSVD patients exhibited significant gray matter atrophy and decreased ReHo and fALFF in secondary olfactory regions, indicating focal structural and functional compromise. However, in multivariable regression models including these regional measures, none significantly predicted UPSIT scores except the ReHo of the parahippocampal gyrus. This dissociation between focal olfactory-pathway injury and olfactory identification suggests that, unlike primary neurodegenerative conditions, olfactory identification deficits in CSVD are not driven by direct olfactory-cortex damage[34].

Recent studies in neurodegenerative disorders demonstrate that successful odor identification requires engagement of neocortical networks[11]. Resting-state network analyses revealed widespread inter- and intra-network connectivity alterations in CSVD, especially within the triple-network model comprising the SN, pDMN, and FPN. Intra-network analyses revealed decreased FCS within key network hubs—namely the dlPFC, precuneus, angular gyrus, insula, and superior parietal lobule. These findings corroborate previous reports that CSVD-related white matter injury disrupts coupling among the SN, pDMN, and FPN [35, 36]. Within the triple-network framework, the SN regulates dynamic switching between the pDMN and the FPN, facilitating transitions from internally directed thought to externally focused, goal-directed behavior [37, 38]. In healthy individuals, the SN and pDMN show a robust negative correlation. In CSVD patients, this negative SN–pDMN correlation is attenuated, indicating a dysfunction in the dynamic switching between externally oriented attention and internally directed representation. Previous studies report that reduced SN–pDMN coupling is associated with emotion-regulation and episodic-memory deficits[39, 40].

Mediation analysis revealed that, in CSVD patients, greater white-matter lesion burden reduces SN–pDMN coupling, which in turn mediates deficits in both olfactory identification and episodic memory. Meanwhile, higher FCS of the dlPFC—a hub of the FPN—is significantly associated with better odor-identification performance and more efficient executive function. Together, these findings suggest that higher-order network integrative capacity supports both cognition and odor identification, highlighting a shared mechanism underlying cognitive and olfactory dysfunction.

These sequential effects indicate that olfactory identification deficits in CSVD arise downstream of network-level disconnection—particularly within memory and executive systems—reflecting higher-order cognitive impairment rather than focal damage to primary olfactory pathways. These findings further indicate that odor-identification tasks constitute a sequential cascade—requiring salient-stimulus detection, memory retrieval, and executive decision-making—reflecting the complex, hierarchical organization of olfactory processing[41].

Longitudinal data underscore the prognostic value of olfactory testing in CSVD. A baseline UPSIT < 20 predicted accelerated MMSE decline, indicating that early detection of hyposmia identifies patients at heightened risk for rapid cognitive deterioration. This temporal linkage supports odor-identification screening to stratify patients for intensified vascular-risk management and targeted

interventions, potentially slowing disease progression before overt deficits emerge.

These findings have several important implications. First, our findings demonstrate that olfactory impairment reflects damage to cognitive function and brain networks in CSVD. Odor identification testing is minimally influenced by educational and demographic factors and, owing to its simplicity, is ideal for the detection of cognitive deficits in both clinical and community settings. Second, because successful odor identification engages both primary olfactory regions and widespread resting-state networks, targeted olfactory–cognitive training protocols could concurrently activate and strengthen these circuits. Such non-pharmacological olfactory–cognitive training interventions may therefore represent a promising approach for enhancing higher-order cognitive functions—particularly memory and executive control—in patients with CSVD[42, 43].

Several limitations merit acknowledgment. First, because overall cognitive levels differed between our CSVD cohort (including the cognitively unimpaired subgroup) and the NC group, this study cannot establish whether olfactory identification decline precedes or follows cognitive impairment. Given the limited sample size, we did not conduct longitudinal prognostic analyses of cognition in the doubly restricted subgroup (education-matched and cognitively unimpaired). Accordingly, we have begun recruiting early-stage, education-matched, cognitively unimpaired CSVD participants to enable more definitive longitudinal analyses. Second, our cohort was recruited from a single institution and included a relatively small sample, which may limit the generalizability of our findings. In addition, we excluded patients with non-lacunar ischemic strokes, which differ from lacunar strokes in pathophysiology, prognoses, and clinical features[44]. Future studies should employ larger, multicenter cohorts with prespecified ischemic-subtype stratification to clarify whether ischemic subtype modifies both the baseline diagnostic utility of olfactory identification and its prognostic value for subsequent cognitive decline.

Conclusion

Olfactory-identification deficits in patients with CSVD reflect disintegration of higher-order cognitive networks, and a baseline UPSIT score below 20 predicts accelerated cognitive decline.

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Author contributions Y.Y. participated in the study design, interpretation of results, and manuscript revision. X.F. participated in the study conception and design, data collection, data analysis, interpretation of results, and manuscript writing. B.X. participated in data curation and the preparation of figures. L.L., Y.H., S.Y. and C.G. participated in data collection. All authors have read and agreed to the published version of the manuscript.

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Data availability The data are available from the corresponding author on reasonable request.

Declarations

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

Ethical approval The study was conducted in compliance with the Declaration of Helsinki and received approval from the Ethics Committee of The First Hospital of Jilin University (protocol code 2016–028, approved on February 22, 2016). All patients signed written informed consent respectively.

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