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RESEARCH ARTICLE

Temporo-frontoparietal hypoconnectivity as a biomarker for isolated language impairment in mild cognitive impairment: A cross-cohort comparison

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Abstract

INTRODUCTION: Whether brain functional connectivity (FC) is consistently disrupted in individuals with mild cognitive impairment (MCI) with isolated language impairment (ilMCI), and its potential to differentiate between MCI subtypes remains uncertain.

METHODS: Cross-sectional data from 404 participants in two cohorts (the Chinese Preclinical Alzheimer's Disease Study and the Alzheimer's Disease Neuroimaging Initiative) were analyzed, including neuropsychological tests, resting-state functional magnetic resonance imaging (fMRI), cerebral amyloid positivity, and apolipoprotein E (*APOE*) status.

RESULTS: Temporo-frontoparietal FC, particularly between the bilateral superior temporal pole and the left inferior frontal/supramarginal gyri, was consistently decreased in ilMCI compared to amnestic MCI (aMCI) and normal controls, which was correlated with semantic impairment. Using mean temporo-frontoparietal FC as a classifier could improve accuracy in identifying ilMCI subgroups with positive cerebral amyloid deposition and *APOE* risk alleles.

DISCUSSION: Temporal-frontoparietal hypoconnectivity was observed in individuals with ilMCI, which may reflect semantic impairment and serve as a valuable biomarker to indicate potential mechanisms of underlying neuropathology.

Lin Huang and Wenjing Hu contributed equally to this study.

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KEYWORDS
Alzheimer's disease, amyloid deposition, functional connectivity, mild cognitive impairment, semantic memory

Highlights

- Temporo-frontoparietal hypoconnectivity was observed in impaired language mild cognitive impairment (ilMCI).
- Temporo-frontoparietal hypoconnectivity may reflect semantic impairment.
- Temporo-frontoparietal functional connectivity can classify ilMCI subtypes.

1 | BACKGROUND

To prevent dementia, there is an increasing focus on early detection of mild cognitive impairment (MCI), which is a phase with cognitive deficits but relatively preserved functional capacity.[1,2] MCI is a heterogeneous condition attributed to diverse etiologies, such as Alzheimer's disease (AD), frontotemporal dementia, and vascular dementia.[3] Through clinical assessment, individuals with MCI can be categorized into various subtypes: amnestic MCI (aMCI), characterized by deficits in episodic memory; impaired language MCI (ilMCI), with a decline in language or semantic memory function; and dysexecutive/mixed MCI with impairment in speed, executive function, or other cognitive abilities.[4] The categorization of distinct MCI subtypes and their associated neural underpinnings is essential for understanding the etiology of the disease, predicting its progression, and guiding the development of early intervention and treatment approaches.[5,6]

There have been numerous studies on aMCI (commonly considered as the prodromal stage of AD), but limited research on ilMCI. The diagnosis of ilMCI is determined by deficits in language/semantic tasks such as picture naming and category verbal fluency tasks, whereas episodic memory function remains relatively preserved.[4,7,8] Semantic memory encompasses an individual's general world knowledge and ability to utilize this knowledge, thereby affecting language processing.[9,10] Given the predominant language/semantic memory deficits in ilMCI, it is crucial to focus on the hub region of the semantic representation network in the human brain, which is reported to be situated in the anterior temporal lobe (ATL).[9–11] The conversion of ilMCI remains uncertain, as some studies suggest a possible progression toward semantic dementia (SD) or atypical AD.[12,13] Distinguishing between these two conditions during the MCI phase poses a significant challenge. SD is a clinical subtype of frontotemporal dementia characterized by impairments in language/semantic memory,[9,13,14] whereas AD typically presents with episodic memory deficits but can also exhibit semantic memory impairments.[15] Identifying ilMCI subgroups that may progress to atypical AD is crucial, particularly in light of the availability of disease-modifying therapies such as amyloid-targeting drugs.[16] The presence of biomarkers, such as cerebral amyloid β (Aβ) deposition and the apolipoprotein E (*APOE*) ε4 allele,[12,17] can help identify ilMCI individuals who may develop into AD.

However, the current classification of ilMCI and aMCI still relies on neuropsychological assessments, which are labor intensive, time consuming, and relatively subjective.[4,18] Although positron emission tomography (PET) can assist in distinguishing MCI due to SD or AD, its practical utility is constrained by financial factors and invasiveness. Neuroimaging, particularly brain magnetic resonance imaging (MRI), holds promise for enhancing diagnostic precision and identifying underlying neuropathological processes. Structural MRI may not be a reliable marker, as both SD and AD exhibit temporal atrophy at MCI stages.[19] Conversely, functional MRI (fMRI) can detect subtle alterations in neural activity and early changes in brain regional connectivity. Therefore, utilizing fMRI techniques to investigate changes in brain functional connectivity (FC) may yield valuable imaging markers. Moreover, an expanding body of literature has employed machine learning algorithms, such as the support vector machine (SVM), to assist in the diagnosis of MCI.[20] The SVM is a supervised learning method that identifies a hyperplane to differentiate between two classes of data by maximizing the margin between the nearest points. This characteristic demonstrates strong robustness, rendering it a suitable model for integrating imaging markers to support MCI classification.

This study aimed to examine specific FC changes in individuals with ilMCI and to determine their effectiveness in classifying MCI subtypes. FC changes were measured using the ATL as seed regions with consistent analytical approaches in two cohorts: the Chinese Preclinical Alzheimer's Disease Study (C-PAS) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants were categorized into ilMCI or aMCI groups and further subdivided based on amyloid positivity and *APOE* status to evaluate the discriminatory power of FC alterations. We aimed to investigate concurrent FC alterations in ilMCI in Chinese and American populations, and their association with cognitive decline. We also assessed the utility of FC changes to differentiate MCI subtypes based on AD-related biomarkers.

2 | METHODS

2.1 | Study design and participants

This cross-sectional study comprised a total of 404 participants enrolled from two cohorts, namely the C-PAS from China[21] and ADNI-2 (adni-info.org) from the United States. Participants underwent a comprehensive assessment, including brain 3.0 T MRI scans and a full set of neuropsychological tests available for MCI diagnosis and

RESEARCH IN CONTEXT

1. **Systematic review**: Recent studies have shown that brain connectivity is consistently disrupted in individuals with amnestic mild cognitive impairment (aMCI), but there is limited research on impaired language MCI (ilMCI). The progression of ilMCI is unclear, with some suggesting that it could lead to semantic dementia or Alzheimer's disease (AD), making differentiation during the MCI stage difficult. Identifying ilMCI subtypes at higher risk of AD is crucial with advancement of new transformative treatments.
2. **Interpretation**: Decreased temporo-frontoparietal functional connectivity in ilMCI in both Chinese and American cohorts suggests early brain changes related to semantic impairment. This connectivity can differentiate ilMCI subgroups with amyloid deposition or apolipoprotein E (*APOE*) risk alleles, serving as a potential biomarker for underlying neuropathological mechanisms.
3. **Future directions**: Future research should investigate larger sample size and the link between temporo-frontoparietal hypoconnectivity and disease progression. In addition, it is crucial to examine how cultural backgrounds impact semantic processing in Eastern and Western populations.

subdivision. Data from C-PAS consisted of 286 participants recruited between 2019 and 2022, who were 50–84 years of age (Cohort 1), and data from ADNI-2 consisted of 118 participants recruited between 2011 and 2016, who were 55–88 years of age (Cohort 2). Both studies received approval from the relevant ethics committees, and all participants provided written informed consent.

The sample size of each group is shown in Figure 1A. The AD group was diagnosed based on the National Institute on Aging–Alzheimer's Association (NIA-AA) 2011 criteria for probable AD dementia.[22] The diagnosis of SD was defined according to the criteria established by Gorno-Tempini[14] and excluded Alzheimer's pathology. The diagnosis of MCI was based on the criteria proposed by Jak/Bondi.[4] Cognitively normal controls (NCs) were determined based on normal cognitive scores, not meeting the criteria for MCI or dementia. Due to a lack of patients diagnosed with SD in ADNI (Cohort 2), individuals with SD were recruited solely from C-PAS (Cohort 1) for the current study. Detailed recruitment and diagnostic criteria can be found in the supporting information.

2.2 | Neuropsychological assessments and MCI subdivision

Participants were screened and diagnosed as MCI at a clinical level based on comprehensive and standardized neuropsychological tests. Both cohorts applied the Montreal Cognitive Assessment (MoCA) to assess global cognition,[23,24] the Auditory Verbal Learning Test (AVLT) for episodic memory,[25,26] the Animal Category Verbal Fluency Test (AFT) and Boston Naming Test (BNT) for language/semantic memory,[27,28] and the Shape Trails Test (STT) or Trail Making Test (TMT) for executive function.[29] Global functional capacity was evaluated by the Functional Assessment Questionnaire and test of activities of daily living (ADL).[30,31] In C-PAS, we additionally evaluated participants' language skills through tasks such as comprehension, grammar, repetition, and naming famous people. Detailed information can be found in our previous publication.[21]

The actuarial neuropsychological method proposed by Jak/Bondi was utilized in this study to diagnose and classify MCI subtypes without specific etiologies[4]: (1) aMCI, characterized by impaired scores on AVLT delayed recall and recognition; and (2) ilMCI, characterized by impaired scores on AFT and BNT. Impaired scores on these neuropsychological tests were defined as greater than 1 standard deviation (SD) below the normative mean. It is important to note that cutoff points for these tests in C-PAS and ADNI may vary due to cultural differences across regions, as evidenced by validation studies. In ADNI, the original English versions of these neuropsychological tests with previously reported cutoff points were utilized.[25,32,33] In C-PAS, the revised Chinese versions of these tests, which have been used extensively with validated cutoffs in the Chinese population, were employed.[18,24] It is notable that only individuals with aMCI and ilMCI were included in this study, whereas patients those with dysexecutive/mixed MCI or incomplete neuropsychological tests were excluded. Additional details can be found in the supporting information.

2.3 | *APOE* status and cerebral amyloidosis

Individuals' *APOE* genotype and amyloid positivity were assessed.[21] *APOE*+ was determined with at least one copy of the *APOE* ε4 allele, and Aβ+ was determined with positive cerebral amyloid deposition through amyloid-PET in C-PAS and either amyloid-PET or cerebrospinal fluid (CSF) in ADNI (see supporting information). We grouped participants from two cohorts based on *APOE* status (*APOE*+ vs APOE−) and cerebral amyloid status (Aβ+ vs Aβ−) to study how FC changes in different MCI subgroups may indicate progression to different types of dementia (SD or AD).

2.4 | MRI scanning and FC analysis

All participants underwent brain MRI on 3 T scanners, including T1-weighted and resting-state fMRI scans. Total intracranial volume (TIV) was calculated for individual variability control. Data pre-processing steps included slice timing, motion correction, normalization, nuisance regression, detrending, smoothing, and temporal band-pass filtering (see supporting information for more details).

For FC analysis, we used the same data processing and statistical analysis procedures to facilitate comparison between the two

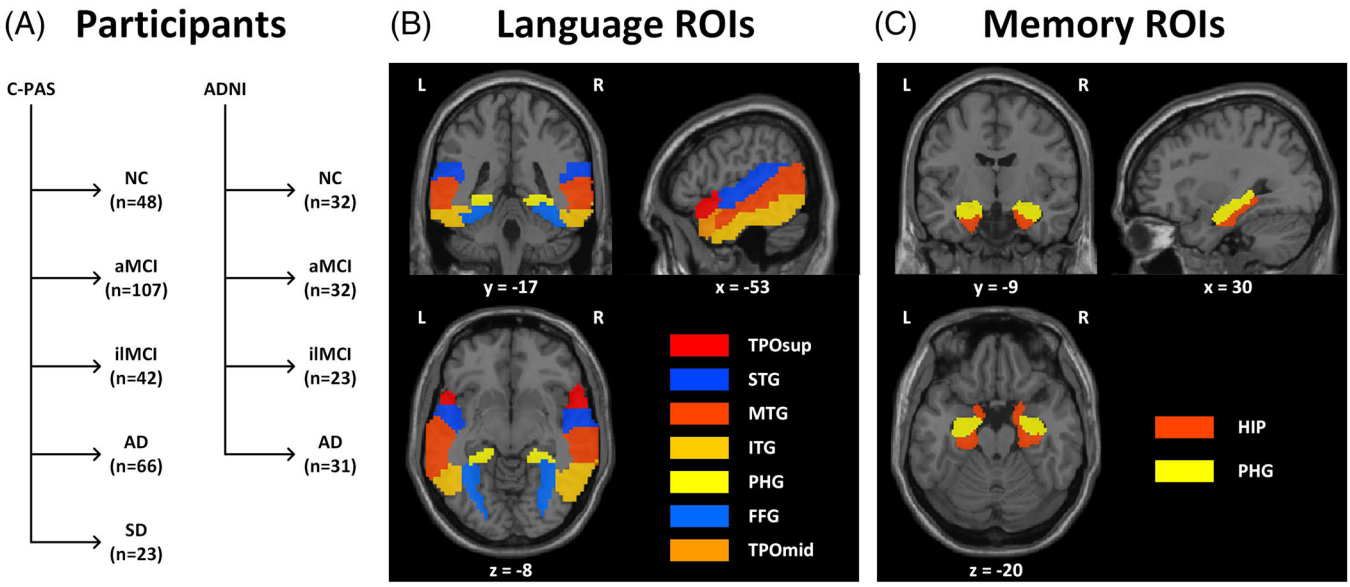

FIGURE 1 Sample size and seed regions for functional connectivity analysis. (A) Number of participants recruited from each cohort. (B) Illustration of the masks for language/semantic ROIs. (C) Illustration of the masks for episodic memory ROIs. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; FFG, fusiform gyrus; HIP, hippocampus; ilMCI, impaired language mild cognitive impairment; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; NC, normal control; PHG, parahippocampal gyrus; ROI, region of interest; SD, semantic dementia; STG, superior temporal gyrus; TPOmid, temporal pole: middle temporal gyrus; TPOsup, temporal pole: superior temporal gyrus.

cohorts, utilizing the DPARSF version 5.2 toolbox[34] (http://rfmri.org/DPARSF). Individual global functional brain networks were created using the automated anatomic labeling (AAL) atlas,[35] dividing the brain into 90 regions, with each region serving as a network node and interregional connectivity serving as network edges/connections. Subsequently, mean time series data were extracted from each segmented region, and pairwise interregional FC was computed using Pearson correlation coefficients. Fisher Z-transformation was used for normalization of the FC matrix.

We selected the bilateral ATL as regions of interest (ROIs) for the language/semantic network; and the bilateral hippocampi (HIP) and parahippocampal gyri (PHG) as ROIs for the episodic memory network (see Figure 1B,C). Based on previously reported neural basis for semantic network[9–11] and the connectional anatomy of the temporal lobe,[36] masks for the ATL included temporal pole: superior temporal gyri (TPOsup), temporal pole: middle temporal gyri (TPOmid), superior temporal gyri (STG), middle temporal gyri (MTG), inferior temporal gyri (ITG), fusiform (FFG), and PHG. Meanwhile, based on previous human fMRI research and the existing knowledge of the critical role of the medial temporal lobe in episodic memory,[37–40] the HIP/PHG were considered as central regions of the episodic memory network. Notably, the main focus of this research was on changes in the language/semantic network, with the episodic memory network analyzed for comparison. By utilizing these language/memory ROIs as specific seeds, we calculated their average connectivity with other brain regions to determine $FC_{language}$ and FC_{memory}. FC alterations were examined in participants with ilMCI or aMCI relative to NCs. Considering that our primary research focus was on the FC alteration in MCI, comparisons to SD/AD groups were included to show trends in different diseases.

2.5 | Statistical analysis

Statistical analysis was conducted using SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) and MATLAB version R2020b (MathWorks, Inc., Natick, MA, USA). The normality of data distribution was assessed through Anderson–Darling and Jarque–Bera tests. Two sample *t*-tests, chi-square tests, or Kolmogorov–Smirnov tests were utilized for comparisons between two groups, and two-way analysis of variance (ANOVA) or nonparametric tests were employed for multiple groups comparisons. Age, sex, years of education, and TIV were regressed as covariates. Furthermore, to integrate data from the two cohorts, we employed the ComBat[41] harmonization technique to address site-specific effects, a methodology that has been utilized in prior scholarly work.[42,43] Partial correlation analysis was conducted between FC values and neuropsychological scale scores, controlling for age, sex, education, and TIV. We combined participants from the two cohorts and used 203 sets of data to train the model for MCI classification. SVM models and leave-one-out cross-validation[20] were utilized to assess classification accuracy between aMCI and ilMCI subgroups, by incorporating FC and T1 volume of bilateral TPOsup as classifiers. Receiver-operating characteristic (ROC) curve analysis and area under the curve (AUC) were used to evaluate the effectiveness of these classifiers ($0.5 \leq AUC < 0.7$, no apparent accuracy; $0.7 \leq AUC < 0.8$, moderate accuracy; $0.8 \leq AUC < 1$, good accuracy). The significance

level was set at $p < 0.05$, and adjustments for multiple comparisons were made utilizing the false discovery rate (FDR) method.

2.6 | Data availability

All data are available from the corresponding author upon reasonable request.

3 | RESULTS

3.1 | Demographics and cognitive performance

Demographic information is shown in Table 1. The ilMCI groups in both cohorts exhibited lower scores in language/semantic memory (as measured by the AFT and BNT) but higher scores in episodic memory (as measured by the AVLT) compared to the aMCI groups, with no statistically significant differences observed in global cognitive assessments. Furthermore, the ilMCI group in C-PAS demonstrated significant semantic deficits (as measured by Famous People Naming tasks), while maintaining intact performance in language comprehension, grammar, and repetition tasks when compared to the aMCI and NC groups. Language/semantic impairment was observed in both AD and SD groups, suggesting challenges in distinguishing between the two conditions at the dementia stage (Table S1). These results indicated a predominant semantic impairment in individuals with ilMCI at an early stage. In addition, there were no statistically significant differences in amyloid positivity or *APOE* status between ilMCI and aMCI in either cohort.

3.2 | Decreased temporo-frontoparietal FC in ilMCI

We conducted FC comparisons in C-PAS and ADNI, respectively. Coexisting FC alterations were observed in ilMCI groups across both cohorts, particularly the connectivity linking the bilateral TPOsup and some frontoparietal regions (see Figure 2). Distinct FC alterations were also identified, with the ilMCI group in C-PAS showing more changes in the MTG areas than those in ADNI. The discrepancy may be attributed to differences in ethnic and cultural backgrounds. In addition, we assessed the whole brain FC alterations in the ilMCI and aMCI groups with and without amyloid deposition in both C-PAS and ADNI, respectively. No statistically significant disparities were found between MCI with and without regressed amyloidosis in the two cohorts (Figure S1). This finding suggests that the observed FC alterations may not be influenced by whether or not amyloidosis is regressed out, which also supports our subsequent analysis.

Among the observed FC alterations, a significant and consistent decline in $FC_{language}$ was identified in ilMCI while remaining intact in aMCI, specifically in the connectivity linking the frontal, parietal, and temporal areas (see Figure 3A). Three consistently decreased temporo-frontoparietal FC connections were identified in ilMCI across two cohorts: the connectivity between the left TPOsup and the left supramarginal gyrus ($FC_{TPOsup.L\text{-}SMG.L}$), the connectivity between the right TPOsup and the opercular part of the left inferior frontal gyrus ($FC_{TPOsup.R\text{-}IFGoperc.L}$), and the connectivity between the right TPOsup and the orbital part of the left inferior frontal gyrus ($FC_{TPOsup.R\text{-}ORBinf.L}$). We computed the mean value of temporo-frontoparietal FC ($FC_{TPOsup.L\text{-}SMG.L}$, $FC_{TPOsup.R\text{-}IFGoperc.L}$, $FC_{TPOsup.R\text{-}ORBinf.L}$) and designated it as an individual's mean temporo-frontoparietal FC in the following analysis.

Conversely, there was no statistically significant difference between ilMCI and aMCI in the connectivity of episodic memory network (Figure 3B). As preconception, a consistent decline in FC_{memory} was observed in AD groups in both cohorts, whereas distinct patterns of $FC_{language}$ were observed in the AD and SD groups (Figure S2). These results suggest the potential utility of $FC_{language}$ rather than FC_{memory} in distinguishing MCI of varying etiologies.

3.3 | Altered temporo-frontoparietal FC in ilMCI subgroups

The above results showed that decreased temporo-frontoparietal FC, namely $FC_{TPOsup.R\text{-}IFGoperc.L}$, $FC_{TPOsup.R\text{-}ORBinf.L}$, and $FC_{TPOsup.L\text{-}SMG.L}$, may be a unique marker for ilMCI and indicate disease progression. To confirm this conjecture, participants from the two cohorts were pooled and stratified into $A\beta \pm$ and *APOE* ± subgroups for further analysis.

In *APOE*− subgroups, $FC_{TPOsup.R\text{-}IFGoperc.L}$, $FC_{TPOsup.R\text{-}ORBinf.L}$, and $FC_{TPOsup.L\text{-}SMG.L}$ were decreased significantly in ilMCI compared to NCs ($FC_{TPOsup.R\text{-}IFGoperc.L}$, $T = 4.03$, $p < 0.001$; $FC_{TPOsup.R\text{-}ORBinf.L}$, $T = 3.86$, $p < 0.001$; $FC_{TPOsup.L\text{-}SMG.L}$, $T = 4.19$, $p < 0.001$; Figure 3C). However, there were no statistically significant differences in the temporo-frontoparietal FC between *APOE*+ subgroups.

Otherwise, irrespective of amyloid deposition, there was a notable decrease in $FC_{TPOsup.L\text{-}SMG.L}$ in ilMCI compared to NCs ($A\beta$+ subgroups, $T = 2.40$, $p = 0.028$; $A\beta$− subgroups, $T = 2.89$, $p = 0.005$; Figure 3D). A significant decrease in $FC_{TPOsup.R\text{-}IFGoperc.L}$ was observed only in $A\beta$+ ilMCI groups ($T = 3.35$, $p = 0.004$, Figure 3D).

The findings indicate that there are differences in temporo-frontoparietal connectivity decline among ilMCI subgroups with and without AD-related biomarkers, which could be used as an imaging biomarker to differentiate between these groups.

3.4 | Association between temporo-frontoparietal FC and cognition

To explore the correlation between temporo-frontoparietal FC and cognitive impairment, specifically semantic deficits in those with ilMCI, data from two cohorts were combined for further analysis. Correlation analysis was conducted between

TABLE 1 Demographic and clinical characteristics.

	Cohort 1					Cohort 2			
Characteristics	NC ($n = 48$)	iIMCI ($n = 42$)	aMCI ($n = 107$)	SD ($n = 23$)	AD ($n = 66$)	NC ($n = 32$)	iIMCI ($n = 23$)	aMCI ($n = 32$)	AD ($n = 31$)
Sex (male/female)	19/29	7/35*,††	48/59	8/15	27/39	15/17	10/13	21/11	15/17
Age	62.17 ± 7.50	64.62 ± 7.47	66.76 ± 6.18	61.70 ± 7.56†	66.06 ± 7.99	72.68 ± 7.86	73.07 ± 6.32	73.75 ± 7.39	72.68 ± 7.86
Education	11.92 ± 2.61	11.26 ± 2.83*	11.43 ± 3.10*	11.70 ± 2.96	10.62 ± 3.43***	16.81 ± 2.67	15.17 ± 2.50	15.69 ± 2.62	16.81 ± 2.67
Total intracranial volume, mm^3	1422825.28 ± 132695.04	1377888.69 ± 129792.04†	1442618.67 ± 145436.40	1430288.09 ± 160367.88	1464507.38 ± 138659.26	1551189.06 ± 155343.53	1527172.17 ± 189803.92	1560196.88 ± 178043.75	1551189.06 ± 155343.53
MoCA	26.73 ± 1.69	21.26 ± 2.56***	21.92 ± 3.33***	13.24 ± 3.54$^{***,\#\#\#,\dagger\dagger\dagger}$	11.55 ± 4.82$^{***,\dagger\dagger\dagger,\#\#\#}$	26.00 ± 1.95	21.30 ± 4.15***,†	23.25 ± 2.58***	16.50 ± 5.46$^{***,\dagger\dagger\dagger,\#\#}$
AVLT recognition	22.23 ± 1.33	20.79 ± 1.47***,†††	16.73 ± 2.20***	13.04 ± 3.75$^{***,\#\#\#}$	11.67 ± 4.38$^{***,\dagger\dagger\dagger,\#\#\#}$	13.47 ± 1.87	10.35 ± 4.01***,†††	6.16 ± 2.48***	6.19 ± 3.99$^{***,\#\#\#}$
AVLT delayed recall	6.06 ± 1.78	3.93 ± 2.48***,†††	1.54 ± 1.46***	0.91 ± 1.47$^{***,\#\#\#,\dagger\dagger\dagger}$	0.88 ± 1.27$^{***,\dagger,\#\#\#}$	7.00 ± 3.83	2.96 ± 4.46**	1.16 ± 1.63***	0.23 ± 0.62$^{***,\#}$
AFT	17.50 ± 3.11	10.17 ± 2.43***,†††	14.78 ± 3.72***	6.61 ± 3.50$^{***,\#\#\#,\dagger\dagger\dagger}$	8.89 ± 3.46$^{***,\dagger\dagger\dagger,\#}$	21.16 ± 3.79	11.61 ± 2.66***,†††	18.22 ± 4.32**	13.48 ± 5.46***,†††
BNT	24.98 ± 2.94	14.79 ± 6.52***,†††	23.41 ± 2.80*	6.74 ± 4.16$^{***,\#\#\#,\dagger\dagger\dagger}$	8.21 ± 8.91$^{***,\dagger\dagger\dagger,\#\#\#}$	28.31 ± 1.60	21.35 ± 4.44***,†††	28.34 ± 1.73	22.81 ± 5.79$^{***,\dagger\dagger\dagger,\#}$
STT/TMT part A	41.94 ± 10.49	50.17 ± 16.37*	57.53 ± 18.84***	79.09 ± 36.58$^{***,\#\#}$	132.76 ± 47.62$^{***,\dagger\dagger\dagger,\#\#\#}$	32.53 ± 7.87	44.39 ± 16.75**,†	34.50 ± 9.74	73.77 ± 35.59***,†††
STT/TMT part B	113.58 ± 30.98	139.57 ± 40.67*,†	151.65 ± 37.71***	170.35 ± 70.96***	264.64 ± 59.74$^{***,\dagger\dagger\dagger,\#\#\#}$	78.00 ± 25.88	139.65 ± 83.38**	104.50 ± 57.25	219.65 ± 91.33***,†††
Cerebral amyloid positivity	5/43 (11.6%)	5/18 (27.8%)	20/44 (45.5%)**	0$^{***,\#\#\#,\dagger\dagger\dagger}$	45/60 (75%)$^{***,\dagger\dagger,\#\#\#}$	5/13 (38.5%)	4/6 (66.7%)	6/13 (46.2%)	10/14 (71.4%)*
APOE ε4 carrier rate	5/48 (10.4%)	8/42 (19.0%)	33/107(30.8%)**	/	34/66 (51.5%)$^{***,\dagger\dagger,\#\#}$	10/32 (31.3%)	9/23 (39.1%)	17/32 (53.1%)	27/31 (87.1%)$^{***,\dagger\dagger,\#\#\#}$

Note: Data are presented as mean ± standard deviation. *Compared with NCs, $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$; †compared with aMCI, $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, and $^{\dagger\dagger\dagger}p < 0.001$; $^{\#}$compared with iIMCI, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$.

Abbreviations: AD, Alzheimer's disease; AFT, Animal Fluency Test; aMCI, amnestic mild cognitive impairment; *APOE*, apolipoprotein E; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; iIMCI, impaired language mild cognitive impairment; MMSE, Mini-Mental State Examination, MoCA, Montreal Cognitive Assessment; NC, cognitively normal control; SD, semantic dementia; STT, Shape Trails Test; TMT, Trail Making Test.

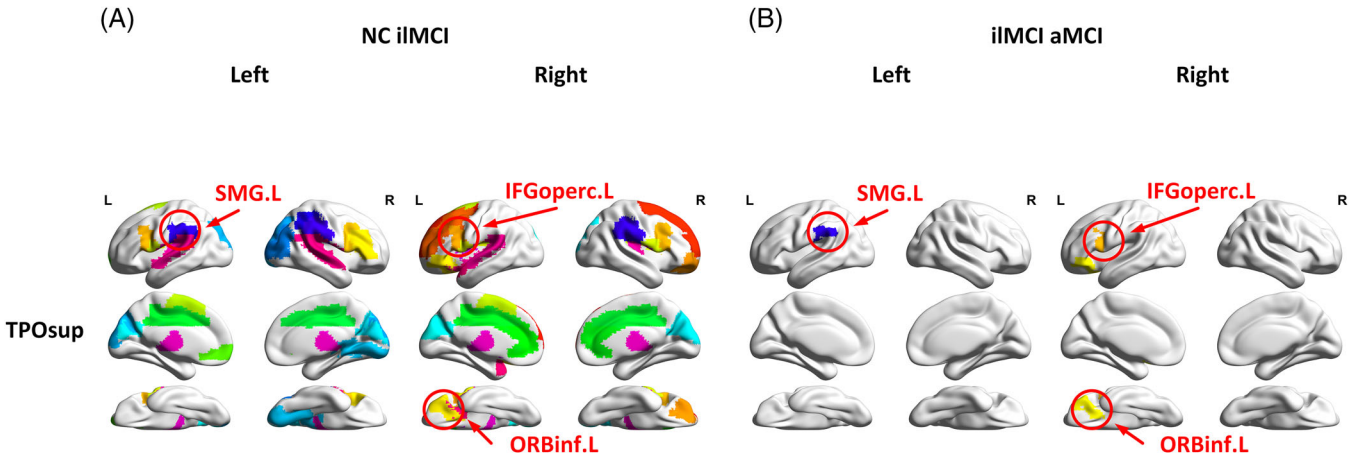

FIGURE 2 Altered functional connectivity in ilMCI to coexist in two cohorts. (A) Brain regions exhibit altered functional connectivity in ilMCI compared to NCs. (B) Brain regions exhibit altered functional connectivity in ilMCI compared to aMCI. Two-sample *t*-test, FDR-corrected. aMCI, amnestic mild cognitive impairment; FDR, false discovery rate; IFGoperc, inferior frontal gyrus, opercular part; ilMCI, impaired language mild cognitive impairment; NC, normal control; ORBinf, inferior frontal gyrus, orbital part; SMG, supramarginal gyrus; TPOsup, temporal pole: superior temporal gyrus.

temporo-frontoparietal FC ($FC_{TPOsup.R\text{-}IFGoperc.L}$, $FC_{TPOsup.R\text{-}ORBinf.L}$, $FC_{TPOsup.L\text{-}SMG.L}$) and their mean values, referred to as an individual's mean temporo-frontoparietal FC, with cognitive scores.

Positive correlations have been observed between both $FC_{TPOsup.R\text{-}IFGoperc.L}$, $FC_{TPOsup.R\text{-}ORBinf.L}$, $FC_{TPOsup.L\text{-}SMG.L}$ and mean temporo-frontoparietal FC with cognitive performance on the MoCA, AFT, and BNT, after controlling for age, sex, education, and TIV (Figure 4A). The findings suggest a notable relationship between decreased temporo-frontoparietal FC and deficits in semantic processing. Subsequent subgroup analysis revealed that $FC_{TPOsup.R\text{-}ORBinf.L}$ was found to be associated with BNT scores in both *APOE*+ and Aβ+ ilMCI individuals, possibly as a biomarker for language/semantic impairment due to AD pathology (Figure 4B).

3.5 | Diagnostic power of mean temporo-frontoparietal FC to classify MCI subtypes

To differentiate between ilMCI due to SD from aMCI due to AD, we conducted an ROC analysis to classify between ilMCI (Aβ−) and aMCI (Aβ+) subgroups. The classification accuracy based on mean temporo-frontoparietal FC exceeded that of the structural volume of superior temporal pole (AUC = 0.805 vs 0.636; Figure 5A).

For ilMCI subgroups, the classification accuracy of mean temporo-frontoparietal FC outperformed that of superior temporal pole volume in distinguishing between Aβ+ and Aβ− groups (AUC = 0.733 vs 0.563; Figure 5B), *APOE*+ and *APOE*− groups (AUC = 0.708 vs 0.521; Figure 5C), as well as APOE+Aβ+ and APOE−Aβ− groups (AUC = 0.810 vs 0.581; Figure 5D).

These results indicate that measurement of the mean temporo-frontoparietal FC could improve diagnostic accuracy of various MCI subtypes, better than T1 volumes.

4 | DISCUSSION

The present research has identified a consistent decrease in functional temporo-frontoparietal connectivity in MCI who exhibit isolated language impairment in two separate cohorts. In addition, these FC changes were found to be significantly correlated with individuals' language/semantic abilities, and may help identify MCI subtypes at higher risk for Alzheimer's pathology. This is the first study to demonstrate shared temporo-frontoparietal hypoconnectivity in ilMCI and its diagnostic utility in both Western and Eastern populations.

The concept of semantic memory was introduced initially by Tulving to describe a person's repository of general world knowledge.[9] It can be tested through picture naming and object recalling tasks.[7] Unlike episodic memory, which tends to decline with age, semantic memory usually remains stable or improves throughout the lifespan.[44,45] Semantic cognition is the ability to use and generalize semantic knowledge, supported by two interacting neural systems: representation and control.[10] Semantic representation forms conceptual knowledge through a network centered in the ATL, whereas semantic control is implemented within a distributed neural network involving the frontal and temporoparietal regions.[10] In the stage of dementia, changes in ATL connectivity have been observed in patients with SD,[46–49] but there is limited evidence in patients with MCI. Our study observed that individuals with ilMCI exhibited predominately lower scores on tests related to semantic memory, such as naming objects and recognizing famous people, whereas their language comprehension, repetition, and grammar skills remain relatively intact. Thus these individuals can be considered a typical representation of patients with semantic deficits during the MCI stage.

In this study, a reduction in temporo-frontoparietal FC was observed in patients with ilMCI, specifically the connectivity between bilateral TPOsup and the left IFG/SMG regions. This finding was

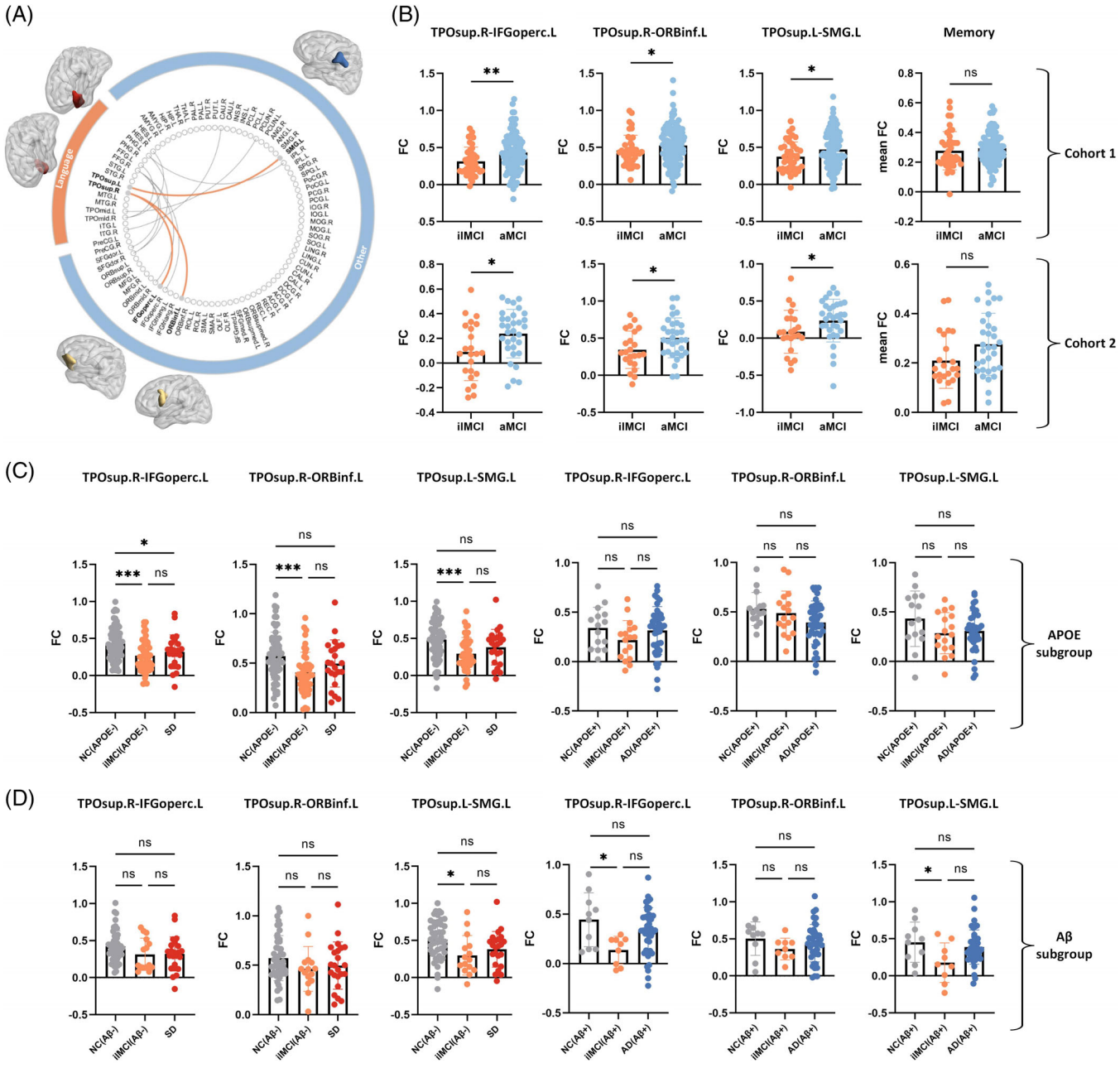

FIGURE 3 Group comparisons for functional connectivity in two cohorts. (A) Functional hypoconnectivity in iIMCI to coexist in two cohorts. (B) Functional connectivity comparisons between iIMCI and aMCI. (C) Functional connectivity comparisons in *APOE* ± subgroups. (D) Functional connectivity comparisons in Aβ ± subgroups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Aβ ± , amyloid beta positive/negative; AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; *APOE* ± , apolipoprotein E ε4 carrier/noncarrier; FC, functional connectivity; IFGoperc.L, left inferior frontal gyrus, opercular part; iIMCI, impaired language mild cognitive impairment; NC, normal control; ORBinf.L, left inferior frontal gyrus, orbital part; SD, semantic dementia; SMG.L, left supramarginal gyrus; TPOsup.L, left temporal pole: superior temporal gyrus; TPOsup.R, right temporal pole: superior temporal gyrus.

consistent across both Chinese and American cohorts, and the FC decline was found to be correlated with the patients' semantic impairment. These results support the key role of temporal and frontoparietal areas in semantic cognition. Prior fMRI studies have shown that the temporopolar cortex is functionally connected to orbitofrontal regions, whereas the superior ATL is linked to auditory and premotor areas.[50–52] The temporal pole, also a subregion of ATL, is involved in semantic processing, particularly for visual and auditory object characteristics.[50,53] Some studies also suggest that frontal and parietal regions may play a crucial role in the acquisition and manipulation of semantic knowledge.[54,55] For instance, both the left IFG and intraparietal sulcus regions have been reported to be involved in semantic control tasks in cognitively unimpaired individuals.[56–58] Furthermore, transcranial magnetic stimulation (TMS) applied to

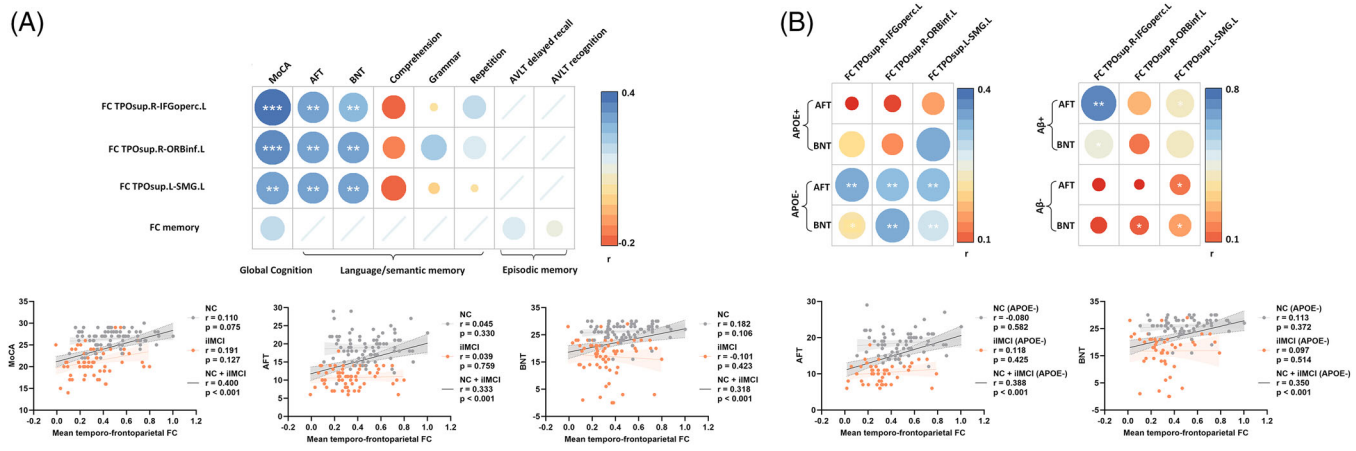

FIGURE 4 Association between functional connectivity and cognitive scores. (A) Correlation between functional connectivity and cognitive scores across two cohorts. (B) Correlation between functional connectivity and cognitive scores in subgroups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. A$\beta \pm$, amyloid beta positive/negative; AFT, Animal Verbal Fluency Test; *APOE* $\pm$, apolipoprotein E $\varepsilon 4$ carrier/noncarrier; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; BVMT, Brief Visuospatial Memory Test; FC, functional connectivity; IFGoperc.L, left inferior frontal gyrus, opercular part; iIMCI, impaired language mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NC, normal control; ORBinf.L, left inferior frontal gyrus, orbital part; SMG.L, left supramarginal gyrus; TPOsup.L, left temporal pole: superior temporal gyrus; TPOsup.R, right temporal pole: superior temporal gyrus.

frontoparietal regions such as the SMG could transiently disrupt semantic functioning, underscoring the significance of these areas in semantic processing.[59–61] Task-based fMRI meta-analysis also confirms the presence of intrinsic connectivity language networks in the human brain, including the dorsal articulatory-phonological network (involving IFG and SMG) and the ventral semantic network (involving the anterior middle temporal and angular gyrus).[62] These studies are in line with the results of our study, providing further validation.

Another significant finding of this research is that temporo-frontoparietal FC alterations can effectively distinguish iIMCI subgroups with or without AD-related biomarkers. Given the distinct cognitive impairments and disease progression, accurate classification of different MCI subtypes is crucial in both clinical practice and cognitive neuroscience. On the one hand, aMCI is characterized by deficits in episodic memory and often transforms to typical AD.[63] Functional neuroimaging shows that a successful memory recollection is related to a core memory network involving the HIP.[64] This study found decreased connectivity in the "memory network" but preserved connectivity in the "language network" in aMCI compared to cognitively unimpaired individuals. However, no significant difference in HIP/PHG connectivity was observed between aMCI and iIMCI, indicating limited discrimination efficiency in "memory network." On the other hand, individuals with iIMCI have significant impairments on language/semantic tasks and relatively preserved function on episodic memory tests. Currently, the clinical outcome and prognosis of this MCI subtype are unclear and debated. Patients with iIMCI may progress to frontotemporal dementia or atypical AD,[65–67] but distinguishing between the two at this MCI stage is challenging with a lack of biomarkers. In this study, we found that decreased functional temporo-frontoparietal connectivity could effectively identify iIMCI with likelihood to progress to SD or atypical AD. Prior studies have shown that semantic performance in patients with MCI can predict AD conversion and amyloid positivity,[7,68,69] but none have used brain connectivity to track disease progression. Our findings shed light on the pathological processes and potential progression of MCI individuals with significant language/semantic deficits.

Yet, several limitations should be noted. First, the disparities in age, ethnic background, and case source between C-PAS and ADNI have resulted in discrepancies in amyloid positivity and *APOE* $\varepsilon 4$ carrier rates.[70,71] To promote consistency in data analysis between the two databases, stringent recruitment criteria, including the completion of high-quality fMRI scans and neuropsychological tests, have been implemented, leading to a decrease in sample size and potentially diminishing the statistical power. Given the disparities observed between the two databases, we conducted a stratified analysis by categorizing individuals into subgroups and performed regression analysis with demographic factors as covariates. We posit that the differences in proportions between the two cohorts may not affect our primary findings significantly. Future research should aim to increase the sample size and further investigate whether iIMCI individuals exhibiting AD-related biomarkers and temporo-frontoparietal hypoconnectivity are at higher risk for developing atypical AD. Second, this study was observational and cross-sectional. The researchers did not directly observe alterations in brain function during semantic tasks, and we did not investigate the long-term progression of iIMCI to ascertain whether FC changes may play a role in predicting or contributing to subsequent decline into dementia. It is recommended that future studies employ a combination of task-state brain imaging and TMS to gain a more comprehensive understanding of the relationship between FC changes and semantic decline. Third, although individuals were categorized into subtypes of iIMCI and aMCI using neuropsychological criteria, it should be noted that they are not entirely dissociated. Emerging evidence suggests that a semantic disorder can also be

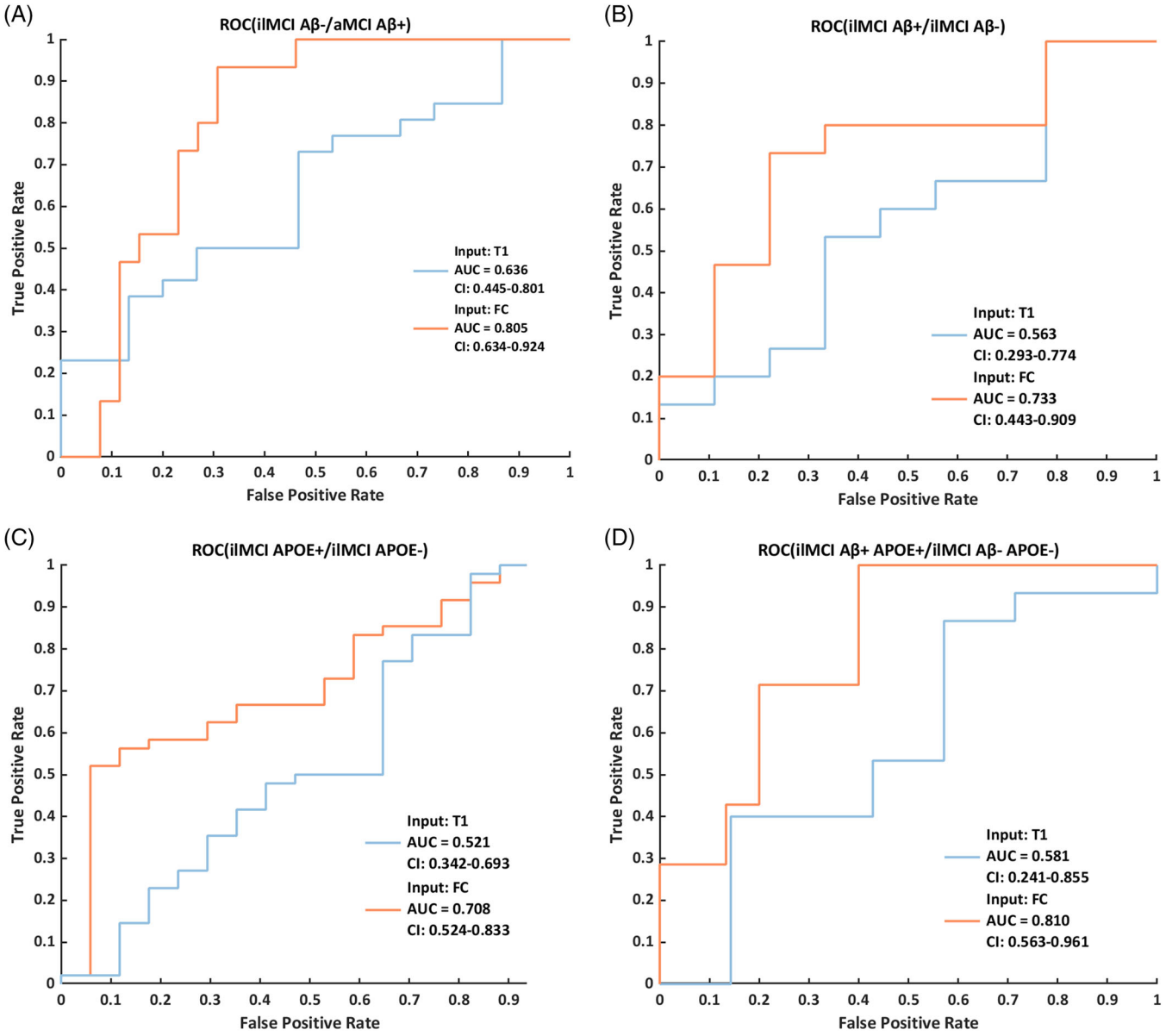

FIGURE 5 Classification accuracy between MCI subtypes. (A) ilMCI (Aβ−) versus aMCI (Aβ+). (B) ilMCI (Aβ+) versus ilMCI (Aβ−). (C) ilMCI (*APOE*+) versus ilMCI (*APOE*−). (D) ilMCI (*APOE*+Aβ+) versus ilMCI (*APOE*−Aβ−). A$\beta\pm$, amyloid positive/negative; AFT, Animal Verbal Fluency Test; APOE $\pm$, apolipoprotein E ε4 carrier/noncarrier; AUC, area under the curve; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CI, confidence interval; FC, functional connectivity; ilMCI, impaired language mild cognitive impairment; ROC, receiveroperating characteristic; T1, volume of superior temporal pole.

observed in individuals with aMCI.[7] Previous studies did not always specify whether MCI individuals exhibited cognitive impairment in a single domain or multiple domains, with the latter potentially indicating a higher risk of progression to dementia.[72] Therefore, future research should investigate abnormal patterns of brain function in individuals with multiple domain MCI and their relationship to cognitive decline. Last is about cultural differences. The study identified similar brain changes in individuals with ilMCI from China and the United States, yet did not investigate the potential influence of cultural disparities on semantic processing. Subsequent research should investigate the impact of cultural backgrounds on semantic processing in Eastern and Western populations.

In conclusion, this study found that individuals with ilMCI from both the Chinese and American cohorts share similar functional temporo-frontoparietal hypoconnectivity. This hypoconnectivity is linked to language/semantic impairment and could help identify MCI subtypes with potential AD pathology, thereby improving our understanding of brain mechanisms and potentially leading to personalized treatments for MCI.

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CONFLICT OF INTEREST STATEMENT

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

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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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