Human Brain Mapping of Homotopic Functional Affinity

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Abstract

Spatially corresponding areas in the left and right hemispheres of the human brain, also known as homotopic brain regions, often exhibit functional similarities, i.e., functional homotopy. To understand the principles and mechanisms of functional homotopy in human psychological behavior, this paper proposes a method for studying functional homotopy in the human brain: homotopic functional affinity. This method quantifies the functional affinity of homotopic brain regions by calculating the cosine distance of whole-brain functional connectivity patterns of homotopic regions. Using the whole-brain functional MRI database from the Human Connectome Project in the United States and China, we first mapped the homotopic functional affinity atlas with "700 milliseconds - 2 millimeters" spatiotemporal precision, assessing its test-retest reliability for individual differences. Subsequently, we located three specific areas in the human temporo-parietal junction through systematic analysis of this atlas, discovering their hemispheric lateralization patterns and revealing their functional associations with attention, language, and social cognition. Lastly, through multimodal brain atlas correlation calculations, we further explored the correlation of human brain homotopic functional affinity with genetics, evolution, structural, and functional organizational distribution. In summary, our proposed method of homotopic functional affinity provides a reliable and valid functional measurement atlas for population neuroscience research.

Keywords: Homotopic Brain Regions, Functional Homotopy, Affinity, Connectome, Temporo-Parietal Junction, Cultural Neuroscience

Introduction

Homotopic brain regions refer to areas in the human brain that correspond in mirror positions between the left and right hemispheres, originating from and evolving with respect to equivalent structures [1]. The corpus callosum provides a direct structural connection for information integration between homotopic regions, resulting in a high similarity of functional activity between them, exhibiting homotopic characteristics [2, 3]. At the same time, the specific connections of homotopic regions with other functional network areas promote hemisphere-specific information processing in homotopic regions [4]. This hemispheric functional organization is significant for the evolution of cognitive functions [5, 6]. The functional integration and specificity of homotopic regions play an indispensable role in basic perceptual, advanced cognitive, and behavioral processes. Primary perception requires higher functional integration between homotopic areas, hence showing stronger homotopic characteristics, while advanced cognitive processing displays a clear hemisphere preference, resulting in lower levels of functional homotopy [7-9]. Clinical comparative studies have found that functional homotopy is abnormal in brain diseases related to cognitive and mental disorders, suggesting potential applications of functional homotopy research in promoting brain health [10, 11].

Functional homotopic connectivity, based on resting-state functional MRI data, quantifies interhemispheric functional collaboration by directly calculating the Pearson correlation between time series of homotopic brain regions, showing considerable reliability [13, 14]. This method has provided preliminary evidence for hemisphere collaboration or lateralization and its cognitive and health significance [15-17]. However, this calculation method is data-driven and lacks guidance from brain connectivity theories. The dual-factor generative theory of the brain's connectome [18], through empirical observations of brain connectomes across different species and age groups, has found that brain connectivity patterns are significantly influenced by two factors: spatial distance between connected brain regions (geometric properties) and homophilic attraction of connectivity patterns between them (topological properties) [19, 20]. Functional homotopic connectivity only emphasizes the spatial geometric properties of homotopic regions, ignoring the homophilic pattern of homotopic regions, thus failing to effectively characterize the complete network connectivity pattern similarity between homotopic regions, limiting precise quantification and interpretation of functional homotopy.

Existing large-scale studies of human brain functional networks have shown the importance of characterizing the homophilic properties of network connectivity patterns between brain regions. Yeo and colleagues, by revealing the organizational architecture of the human brain's resting-state functional connectome, defined macro-scale cortical functional networks and a series of functionally homophilic parcellations [21-23]. Based on this, they further developed homotopic parcellations for brain functions [24], providing prior functional information for homotopic regions. Finn and colleagues proposed the fingerprint method of the human brain's functional connectome [25], defining each brain region's network connectivity pattern as its "functional fingerprint", revealing the unique fingerprints of different individuals and brain regions, providing new perspectives for comparing the functional homophilic attraction of different brain regions [26]. Subsequently, Margulies and colleagues defined the functional fingerprint similarity between brain regions as "affinity", studying the whole-brain affinity matrix (i.e., network connectivity pattern homophilic matrix) by dimension reduction methods of the brain's functional connectome, revealing the intrinsic dimensions of the functional organization of the adult human brain's connectome, i.e., functional connectivity gradients [27]; further studies [28, 29] have found that the gradient characteristics of the human brain's functional connectome organization are correlated with evolution, development, behavior, and psychopathology.

Based on the dual-factor generative theory of the connectome, this paper proposes a method for calculating homotopic functional affinity in the human brain, characterizing functional homotopy through the functional fingerprint affinity between homotopic brain regions. We first calculated the homotopic functional affinity atlas with high spatiotemporal precision based on large data from resting-state functional MRI of the Human Connectome Project in China and the United States, then assessed the test-retest reliability of this method in measuring individual differences using a linear mixed model, demonstrating the reliability of the homotopic functional affinity method in individual difference measurement. Finally, through cognitive association analysis of areas of interest and multimodal whole-brain atlas correlation analysis, we verified the validity of the homotopic functional affinity method. This method enriches the methodology of functional homotopy research, providing a more reliable and valid neuroimaging measurement atlas of human brain functional individual differences for population neuroscience research.

1 Method

1.1 Sample Selection

1.1.1 Human Connectome Project (HCP) Dataset, USA

The study utilized resting-state functional MRI data and task-based functional MRI data (during language processing and social cognition tasks) of 339 unrelated subjects (male/female = 157/182, age = 28.64 ± 3.70 years) from the HCP dataset [30]. The data were collected using a custom 3T Siemens Skyra Connectome MRI scanner, with a repetition time of 720 milliseconds, echo time of 33.1 milliseconds, an in-plane field of view of 208 mm × 180 mm, 72 slices, a flip angle of 52 degrees, and voxel size of 2 mm × 2 mm × 2 mm. Each subject underwent four resting-state fMRI scans over two days (two scans per day with phase encoding directions from left to right and right to left). A single resting-state fMRI scan included 1200 time points, lasting 14.4 minutes. The cognitive behavioral paradigms for the tasks are described in 1.2, with two scans in opposing phase encoding directions (left to right and right to left) for each task. The single scan duration for the language processing task was approximately 3.8 minutes, containing 316 time points. The social cognition task lasted about 3.3 minutes per scan, containing 274 time points [31].

1.1.2 Chinese Human Connectome Project (CHCP) Dataset

The CHCP dataset, directly benchmarked against the HCP dataset, is a multimodal imaging large dataset based on the Chinese population [32]. The current study included resting-state fMRI data from 217 subjects (male/female = 109/108, age = 22.37 ± 2.88 years) in the CHCP dataset, of which 185 subjects had task-based fMRI data (male/female = 90/95, age = 22.57 ± 2.99 years). The data collection process was similar to HCP, using a 3T Siemens Prisma MRI scanner. Each scan had a repetition time of 710 milliseconds, echo time of 30 milliseconds, and an in-plane field of view of 212 mm × 212 mm. The number of slices, flip angle, and voxel size were the same as the HCP dataset. Resting-state fMRI scans were conducted over two days, with two scans each day in opposite phase encoding directions (from front to back and back to front). Each scan included 634 time points, lasting 7.5 minutes. The behavioral paradigms for language processing and social cognition tasks were consistent with HCP but were adapted into Chinese. Each task included two fMRI scans in opposing directions. The scan duration was nearly identical to HCP, with 321 time points for the language processing task and 278 time points for the social cognition task.

1.2 Cognitive Behavioral Paradigm

1.2.1 Language Processing Task

The language processing task assesses auditory and semantic processing capabilities through two rounds of testing (two scans). Each round consisted of four sets of story tasks and four sets of arithmetic tasks, alternating, with each set lasting approximately 30 seconds. In each story task set, subjects listened to 5-9 sentences from short stories adapted from Aesop's Fables and chose the main theme of the story from two options. Each arithmetic task set involved verbal arithmetic operations, where subjects performed addition or subtraction on two numbers and selected the correct answer from provided options [33]. The auditory and verbal input in arithmetic tasks was similar to story tasks, requiring focused attention but not involving semantic processing, serving as a contrast to the story tasks.

1.2.2 Social Cognition Task

The social cognition task, adapted from the studies of Castelli et al. [34] and Wheatley et al. [35], assessed individual's theory of mind levels through video during two rounds of scanning. Each round included five sets of geometric video tasks (2 sets of social interaction videos and 3 sets of random videos or vice versa) and five sets (each 15 seconds) of fixed gaze tasks. In each geometric video set, subjects watched a 20-second video involving shapes like squares, circles, and triangles. Subsequently, subjects had to decide whether there was social interaction among the movements of these shapes in the video, with three options: present (the movements of the shapes appeared to consider each other's feelings and thoughts), uncertain, and absent (no interaction, movements were random).

1.3 Functional MRI Data Preprocessing

The MRI data used in this study had been preprocessed by the HCP and CHCP teams using their standardized processes and were publicly shared [32, 36]. Thus, only a brief introduction to functional MRI data preprocessing is provided here. Both resting-state and task-based fMRI data preprocessing were completed using the HCP minimal preprocessing pipelines [36]. This included correction for field inhomogeneities and head motion, as well as establishing mappings between individual space and standard space. Data were then mapped to the standard 32k gray matter coordinate space and underwent Gaussian smoothing with a full width at half maximum of 2 millimeters on the cortical surface. Resting-

state fMRI data were high-pass filtered with a threshold of 2000 seconds to remove slow drifts in the time series and underwent independent component analysis-based denoising. Task-based fMRI data were processed for individual task activations, including high-pass filtering with a threshold of 200 seconds (for more information on data preprocessing and dataset comparisons, refer to references [31, 32, 36]).

1.4 Concatenation Processing of Resting-State fMRI Time Series

To reduce noise in resting-state fMRI data and improve the efficiency of large data computations, an incremental group principal component analysis method was used for concatenation processing of the time series of each vertex on the cortex after preprocessing, as referenced in HCP's resting-state functional connectome calculations [37]. The total length of time series for each vertex was slightly shorter than the total number of time points of an individual subject's scan. Group-level connectome maps were calculated using this method, concatenating all subjects' resting-state data. For test-retest reliability analysis, this method concatenated two groups of resting-state fMRI time series for each subject on the same day, thus combining the time series of two-day scans into two groups for each subject, to be used as test and retest data. Moreover, this method concatenated four groups of resting-state fMRI time series for each subject to create an average time series for subsequent analyses of functional homotopic affinity and cognitive activation associations.

1.5 Calculation of Homotopic Functional Affinity Atlas

The HCP standardized gray matter coordinate space provided a spatially symmetric brain template for homotopic calculations, with vertices on the left and right cortical surfaces having the same numbers as homotopic vertices. As illustrated in Figure 1, the first step was to calculate the whole-brain functional connectivity pattern (functional connectivity fingerprint) for each homotopic vertex, representing its degree of temporal synchrony (positive functional connectivity) and asynchrony (negative functional connectivity) with all vertices across the brain. Subsequently, the cosine distance between the functional connectivity fingerprints of a pair of homotopic vertices was calculated to quantify their functional affinity, defined as the functional homotopic affinity at that location. Higher functional homotopic affinity indicates stronger functional homophilic attraction between homotopic vertices; conversely, lower affinity indicates lower homophilic attraction and stronger functional heterogeneity. It should be noted that when calculating cosine distance, the intra-hemispheric connectivity fingerprint and inter-

hemispheric connectivity fingerprint of one vertex must correspond to those of its homotopic vertex. Based on the concatenated time series, group-level homotopic affinity atlases, individual test-retest homotopic affinity atlases, and individual (based on concatenated four groups of resting-state data) homotopic affinity atlases were calculated for both HCP and CHCP datasets. To enhance spatial smoothness and signal-to-noise ratio, all individual-level homotopic affinity atlases were Gaussian-smoothed with a full width at half maximum of 5 millimeters.

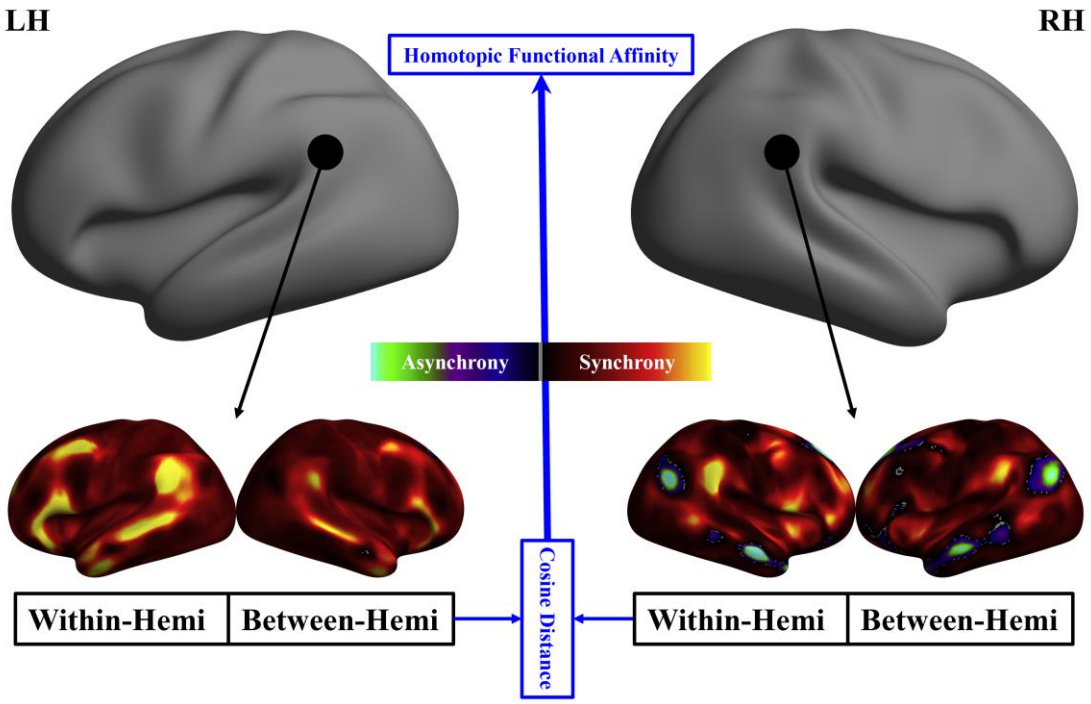

Figure 1: Calculation of Homotopic Functional Affinity. For a pair of homotopic vertices on the brain cortex (the black circles in the left and right hemispheres in the figure, with opposite horizontal coordinates), their whole-brain functional connectivity patterns (functional fingerprints) are calculated separately, quantifying their synchrony (positive correlation of time series) and asynchrony (negative correlation of time series) with vertices across the whole brain. The functional connectivity fingerprints of homotopic vertices are then concatenated in the order of "within-hemisphere connections - inter-hemisphere connections" (as shown in the figure), and their cosine distance (i.e., spatial correlation) is calculated to quantify the functional homotopic affinity at that cortical vertex.

1.6 Test-Retest Reliability Assessment Calculation

The test-retest reliability of the homotopic functional affinity measurement was assessed using a linear

mixed-effects model [38-40]. Firstly, age and gender were considered as covariates to assess the within-subject variability and between-subject variability (1).

$$h_{ij} = \beta_{\alpha} \times \alpha_{0j} + \beta_{e} \times e_{ij} \tag{1}$$

h_{ij} represents the homotopic affinity measurement value for subject *j* during measurement *i*, determined by α_{0j} and the model residual e_{ij}. Here, $\alpha_{0j} = \beta_{\mu} \times \mu_{00} + \beta_{p} \times p_{0j} + \beta_{\text{age}} \times \text{age}_j + \beta_{\text{sex}} \times \text{sex}_j$. μ_{00} as a fixed effect, represents the average of all subjects' test and retest measurements, and age_j and sex_j are the age and gender of subject *j*, p_{0j} is the average of different measurements for subject *j*. α_{0j} varies only with different subjects *j*. After regressing for age and gender, the between-subject variability V_b can be represented by the variability of p_{0j}. When subject *j* is fixed, the model residual e_{ij} comes from the variability between different measurements *i* for subject *j*. Hence, the within-subject variability V_w can be represented by the variability of e_{ij}. By calculating the ratio of between-subject variability to total variability (sum of within-subject and between-subject variability), the intraclass correlation coefficient (ICC) (2) is obtained, serving as the standard for measuring test-retest reliability.

$$ICC = \frac{V_b}{V_b + V_w} \tag{2}$$

The intraclass correlation coefficient of the global mean μ and standard deviation σ of homotopic affinity, as well as the intraclass correlation coefficient for each vertex, were calculated. The calculation of the intraclass correlation coefficient on vertices required individual-level standardization of homotopic affinity values (3). For vertex *k*, its standardized homotopic affinity value h_{kz} is equal to the original homotopic affinity value h_k minus the individual atlas's global mean μ, divided by the global standard deviation σ.

$$h_{kz} = \frac{h_k - \mu}{\sigma} \tag{3}$$

1.7 Validity Verification

1.7.1 Area of Interest Localization Analysis

Based on the brain-wide distribution patterns of homotopic functional affinity and the test-retest reliability levels of individual differences at each vertex in different datasets, the Temporo-Parietal

Junction (TPJ) - an area with high reliability and marked regional differentiation (low affinity) and sample variability - was identified as the area of interest for further analysis of the homotopic affinity atlas. Using the cortical homotopic affinity atlas from HCP, affinity edge detection near TPJ was performed to locate its subregions and extract their whole-brain functional connectivity fingerprints across different datasets, deciphering the source of their functional homotopy differentiation. Meta-analysis based on the Brainmap database (https://www.brainmap.org) [41-43] was conducted to analyze cognitive-behavioral function associations of these TPJ subregions in both hemispheres. Finally, using method in (3), individual homotopic affinity atlases were standardized, extracting the mean normalized homotopic affinity within these subregions and activation levels under cognitive tasks, calculating the Pearson correlation between them, and performing multiple comparison corrections to compare the consistency of these results with meta-analysis findings.

1.7.2 Whole-Brain Multimodal Atlas Correlation Analysis

Using Neuromaps [44], human brain gene expression atlases [45], cortical evolutionary expansion atlases [46], cross-species functional homology index atlases [47], cortical myelination atlases [48, 49], functional connectivity principal gradient atlases [27], and cognitive association principal atlases [50] were extracted. These were transformed into the standard 32k gray matter coordinate space, and the spatial distribution relationship between their mean atlases in both hemispheres and the homotopic functional affinity atlas was modeled and analyzed.

2 Results

2.1 High-Precision Whole-Brain Homotopic Functional Affinity Atlas

The homotopic functional affinity atlas of the human brain exhibited highly consistent spatial distribution characteristics in both the HCP (Figure 2a) and CHCP (Figure 2b) datasets. Specifically, the functional affinity of homotopic brain regions generally decreased along the gradient from "primary cortex to associative cortex": the visual, somatomotor, and auditory functional networks exhibited the highest homotopic functional affinity, while the default mode and frontoparietal control networks had the lowest, with the two (ventral and dorsal) attention networks in between.

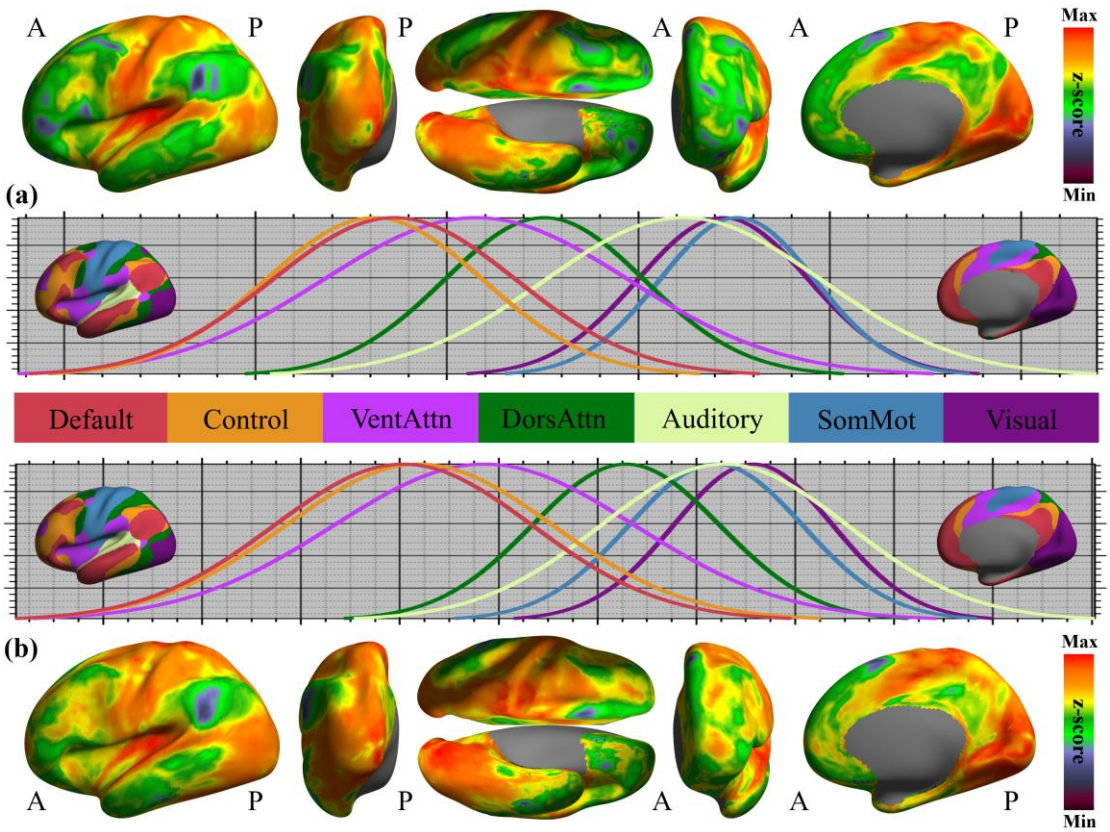

Figure 2: Group-Level Distribution Patterns of Homotopic Functional Affinity in the Human Brain Cortex. Group-level homotopic functional affinity maps of the human brain cortex in the HCP (a) and CHCP (b) datasets are rendered from different perspectives and projected onto the hemispheres (A: anterior, P: posterior). For seven large-scale functional connectivity networks of the human brain [32], Gaussian models were used to fit the distribution of their homotopic affinity.

2.2 Test-Retest Reliability of Individual Differences in Homotopic Functional Affinity

The intraclass correlation coefficient (ICC), ranging from 0-1, was used as a quantitative indicator of the reliability of individual difference measurements, classifying reliability into five different levels: slight, fair, moderate, substantial, and almost perfect [51]. The whole-brain mean and standard deviation of homotopic functional affinity showed moderate measurement reliability (HCP ICC: 0.59 and 0.56, respectively; CHCP ICC: 0.5 and 0.39, respectively). For a whole-brain vertex-level homotopic functional affinity ICC atlas, see Figure 3. In the HCP atlas, 73.58% of the vertices exhibited moderate or higher test-retest reliability, while in the CHCP atlas, 53.56% of the vertices did, reflecting differences in the measurement design of the two datasets (mainly in scanning duration). However, the spatial distribution patterns of the ICC atlases in both datasets were highly similar. Specifically, the test-retest

reliability of associative cortex functional affinity measurements was higher than that of primary cortex, with regions such as the central sulcus, orbitofrontal cortex, and insula, where the blood oxygen level-dependent signals are constrained, showing lower ICCs, although in these regions, the ICCs of HCP functional affinity measurements were higher than those of CHCP.

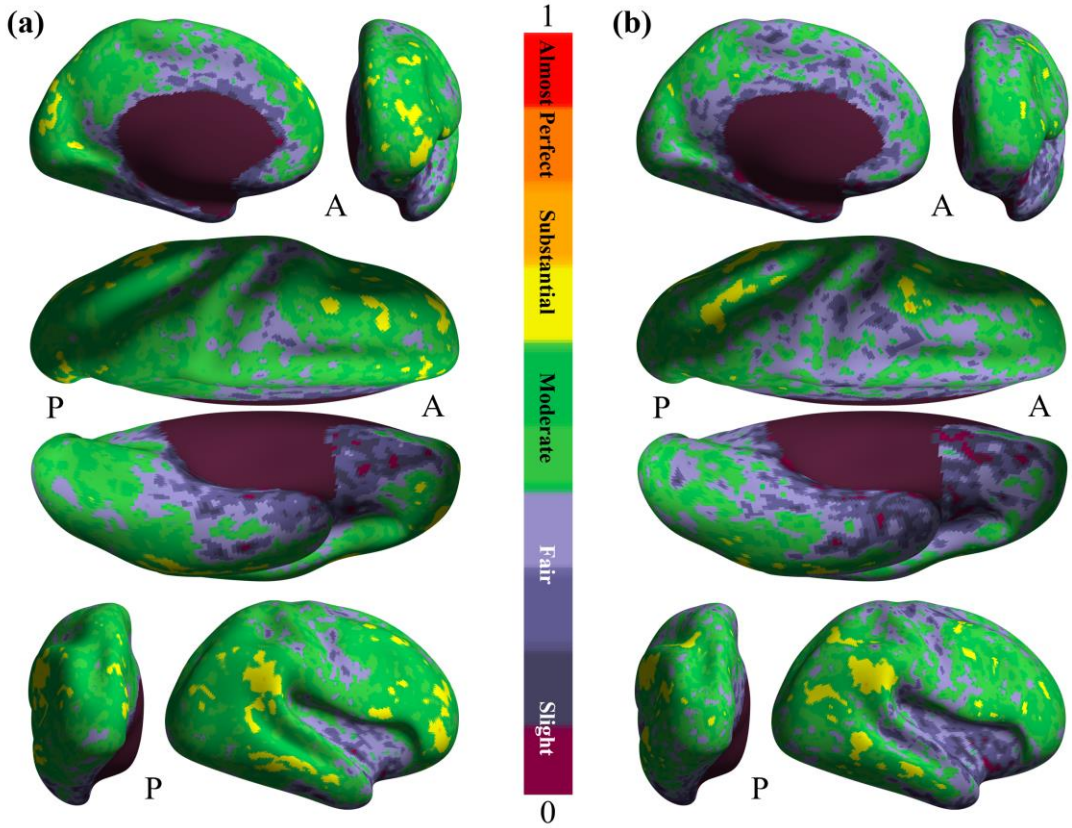

Figure 3: Test-Retest Reliability Maps of Individual Differences in Homotopic Functional Affinity in the Human Brain. A mixed linear model was used to model individual differences in the test-retest datasets of (a) HCP and (b) CHCP, specifically calculating the intraclass correlation coefficient to quantify the test-retest reliability of cortical homotopic functional affinity and visualizing it on the cortical surface (A: anterior, P: posterior).

2.3 Validity of Individual Difference Measurements in Homotopic Functional Affinity

2.3.1 Localization and Validation of Areas of Interest

2.3.1.1 Whole-Brain Functional Connectivity Fingerprints

An edge detection algorithm was used to identify three subregions of the TPJ in the group-level homotopic functional affinity atlas of the HCP: the anterior TPJ subregion (TPJa), the central TPJ

subregion (TPJc), and the posterior TPJ subregion (TPJp).

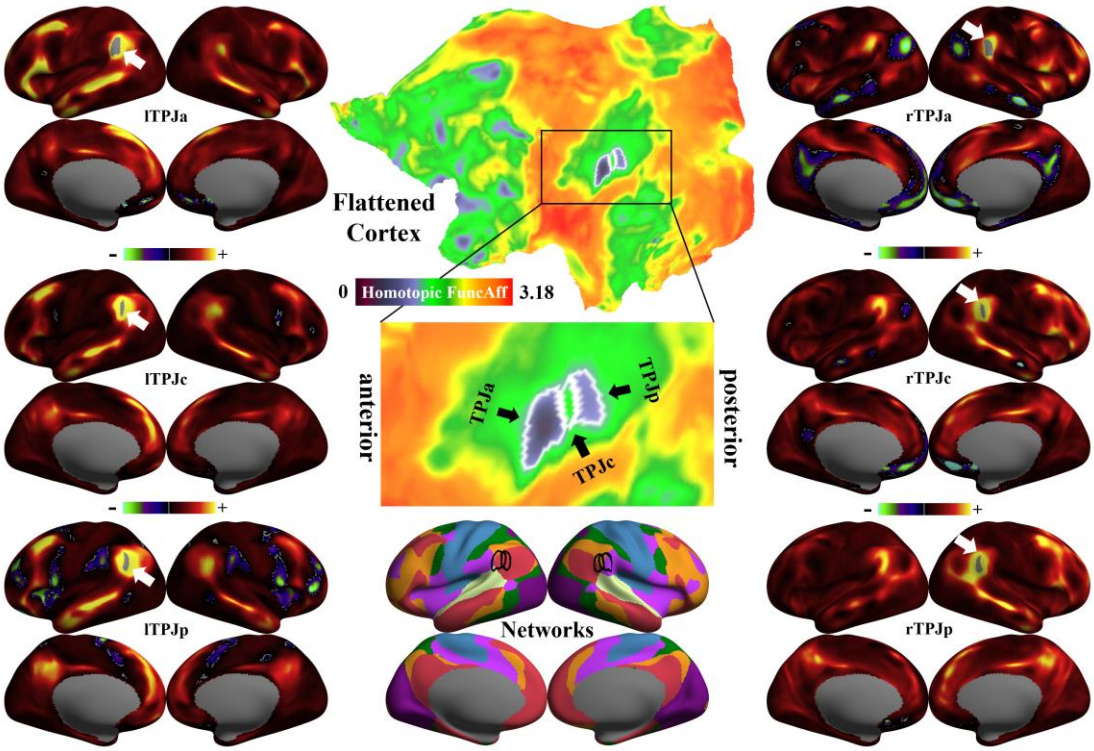

Figure 4: Homotopic Affinity and Functional Connectivity Fingerprints of Subregions in the Human Temporo-Parietal Junction. Based on HCP data, a cortical homotopic functional affinity map focused on the TPJ area through edge detection algorithms, identifying three TPJ subregions: anterior TPJa, central TPJc, and posterior TPJp. The middle column sequentially displays cortical cross-sectional maps of the functional affinity map, boundaries of TPJ subregions, and their positions in seven large-scale functional networks [32]. The left column shows the whole-brain functional connectivity fingerprints of the TPJ subregions in the left hemisphere, while the right column shows those of their homotopic regions.

In the center of Figure 4, the spatial boundary locations of these three subregions are displayed, and on the left and right sides, the cortical functional connectivity fingerprints of their respective hemispheres (HCP dataset) are shown. Specifically, the whole-brain functional connectivity fingerprint of the left TPJa (lTPJa) is characterized primarily by synchrony, reflecting strong connections between the default mode network, frontoparietal control network, and auditory network; whereas the functional connectivity fingerprint of its homotopic region in the right hemisphere (rTPJa) mainly exhibits the strongest

synchrony with the ventral attention network and the strongest asynchrony with the default mode network. The functional connectivity fingerprint of the left TPJp (lTPJp) shows the strongest synchrony with the default mode network and the frontoparietal control network, as well as the strongest asynchrony with the ventral attention network; its homotopic region in the right hemisphere (rTPJp) displays less asynchrony with the default mode network but still the strongest synchrony with the default mode network and frontoparietal control network. The TPJc subregion exhibits a transitional whole-brain functional connectivity fingerprint between TPJa and TPJp. Specifically, the functional connectivity synchrony fingerprint of the left TPJc (lTPJc) is similar to that of lTPJa, but it does not show a network asynchrony fingerprint; the functional connectivity fingerprint of its homotopic region in the right hemisphere (rTPJc) displays a synchrony fingerprint similar to that of rTPJp, and its functional asynchrony fingerprint partially overlaps with that of rTPJa. The bilateral TPJa and TPJp whole-brain functional connectivity fingerprints in CHCP are consistent with those in HCP, but the connectivity fingerprints of the central TPJ subregions are significantly different from those in HCP: the directions in which the bilateral TPJc whole-brain connections converge are different (lTPJc functional connectivity fingerprint is more similar to lTPJp, while rTPJc functional connectivity fingerprint is more similar to rTPJa), and both sides of TPJc have asynchrony fingerprints, resulting in lower similarity between their functional connectivity fingerprints and making it impossible to separate them from TPJa and TPJp, which also have low homotopic functional affinity values, based on the homotopic functional affinity atlas (see Supplementary Material 1 for detailed TPJ whole-brain functional fingerprint results in CHCP).

2.3.1.2 Cognitive Functions of TPJ Subregions and Hemispheric Differentiation

The cognitive functions of the three TPJ subregions and their differentiation across hemispheres as determined by meta-analysis results are shown in Figure 5. Comparing the word cloud results from the meta-analysis in different hemispheres, it can be seen that the cognitive functions of the TPJ subregions in the left hemisphere are more specific than those in the right hemisphere, and the weights of the cognitive processes involved in the TPJ subregions of the right hemisphere are more similar. Like the functional connectivity fingerprints, the cognitive functions related to tasks in each subregion also show transitional characteristics between regions. TPJa is most strongly associated with cognitive functions such as inhibition, attention, and executive control, and in the right hemisphere, a strong association with somatosensory perception was found; TPJc is mainly involved in social cognition, with its right

hemisphere also being more related to somatosensory perception; and TPJp is most strongly associated with language functions, mainly in the left hemisphere, with the strongest association in the right hemisphere being social cognitive functions.

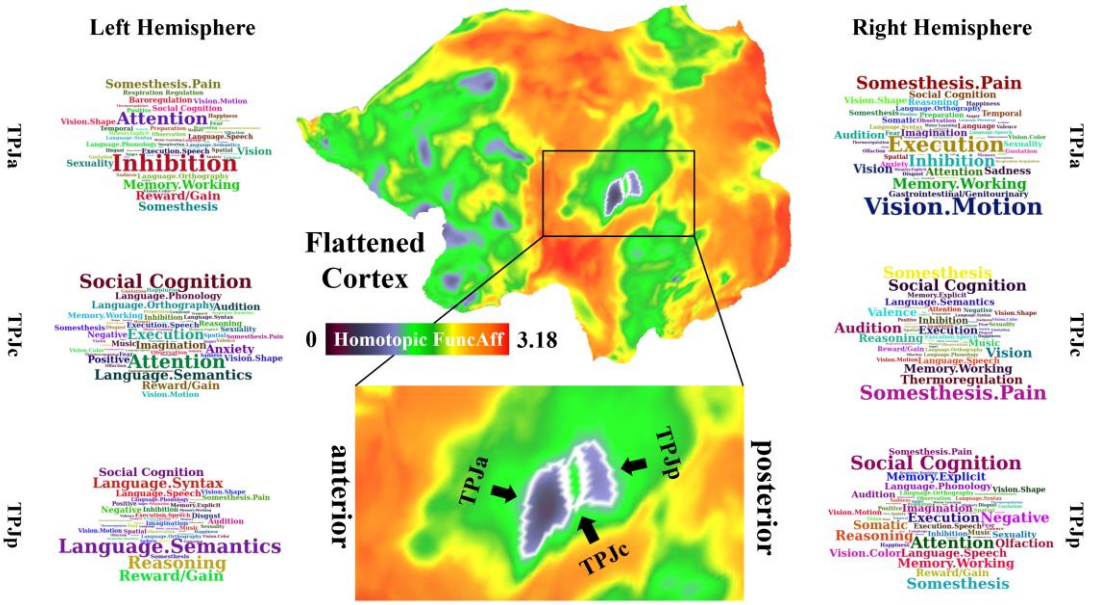

Figure 5: Cognitive Function Meta-analysis Word Clouds for Subregions of the Temporo-Parietal Junction. The middle column sequentially displays cortical cross-sectional maps of the functional affinity map and boundaries of TPJ subregions. The left column shows the cognitive function meta-analysis word clouds for the TPJ subregions in the left hemisphere, while the right column shows those for their homotopic regions.

2.3.1.3 Homotopic Functional Affinity of the TPJ and Cognitive Task Activation

Based on meta-analysis, the correlation analysis of homotopic functional affinity and speech and social cognitive function task activations of the three TPJ subregions in the left and right hemispheres further reveals their respective potential cognitive functions (Table 1). For HCP, during the speech processing task in the "Story - Math" condition, the activations of lTPJa and rTPJp are significantly correlated but oppositely related to their respective homotopic functional affinities. The task activation degrees of the left and right TPJc are significantly and oppositely correlated with their homotopic affinities, corresponding to the aforementioned relationships of lTPJa and rTPJp, respectively. Similar relationships are observed under the "Story" condition, but no significant correlation is observed under the "Math" condition. In the social cognition task, under the "Social Interaction" and "Random" conditions,

significant negative correlations are observed between the activations of rTPJc and rTPJp and their homotopic affinities. For CHCP, the "homotopic affinity - task activation" relationships detected under the "Story - Math" condition in the speech processing task are consistent with those in HCP. Under the "Story" condition, significant negative correlations are observed between the left activations of the three TPJ subregions and their homotopic affinities, and significant correlations are observed between the activations of rTPJc and rTPJp and their homotopic affinities under the "Math" condition. The results obtained in the social cognition task are consistent with the correlation trends in HCP but are not significant.

Table 1: Association of Homotopic Functional Affinity in Temporo-Parietal Junction Subregions with Cognitive Task Activation

Task	Homotopic regions	Condition	HCP		CHCP	
			Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Speech processing	TPJa	Math	-0.03	0.11	0.13	-0.13
		Story	-0.18**	0.09	-0.36**	0.06
		Story - Math	-0.25**	-0.03	-0.36**	0.14
	TPJc	Math	0.07	0.09	-0.01	-0.21*
		Story	-0.02	0.20**	-0.20*	0.11
		Story - Math	-0.16*	0.16*	-0.14	0.24**
	TPJp	Math	0.10	0.03	0.02	-0.26**
		Story	0.06	0.22**	-0.21*	0.15
		Story - Math	-0.06	0.28**	-0.17*	0.28**
Social cognition	TPJa	Interaction	0.09	0.07	0.15	-0.11
		Random	0.11	0.08	0.14	-0.12
		Interaction - Random	-0.01	-0.01	0.05	0.01
	TPJc	Interaction	-0.02	-0.16*	-0.03	-0.07
		Random	-0.04	-0.15*	-0.05	-0.12
		Interaction - Random	0.01	-0.02	0.03	0.03
	TPJp	Interaction	0.05	-0.15*	-0.05	-0.17
		Random	0.04	-0.27**	0.06	-0.14
		Interaction - Random	0.00	0.17*	-0.12	-0.07

* $p < 0.05$, ** $p < 0.01$, corrected within the dataset for FDR (False Discovery Rate).

2.3.2 Multimodal Atlas Association of Cortical Homotopic Functional Affinity Atlas

There are significant correlations between the human brain cortical homotopic functional affinity atlas and the six major atlases included (Figure 6 shows the HCP association results, and the topographic maps of the correlation analysis for HCP and CHCP can be found in the Supplementary Material).

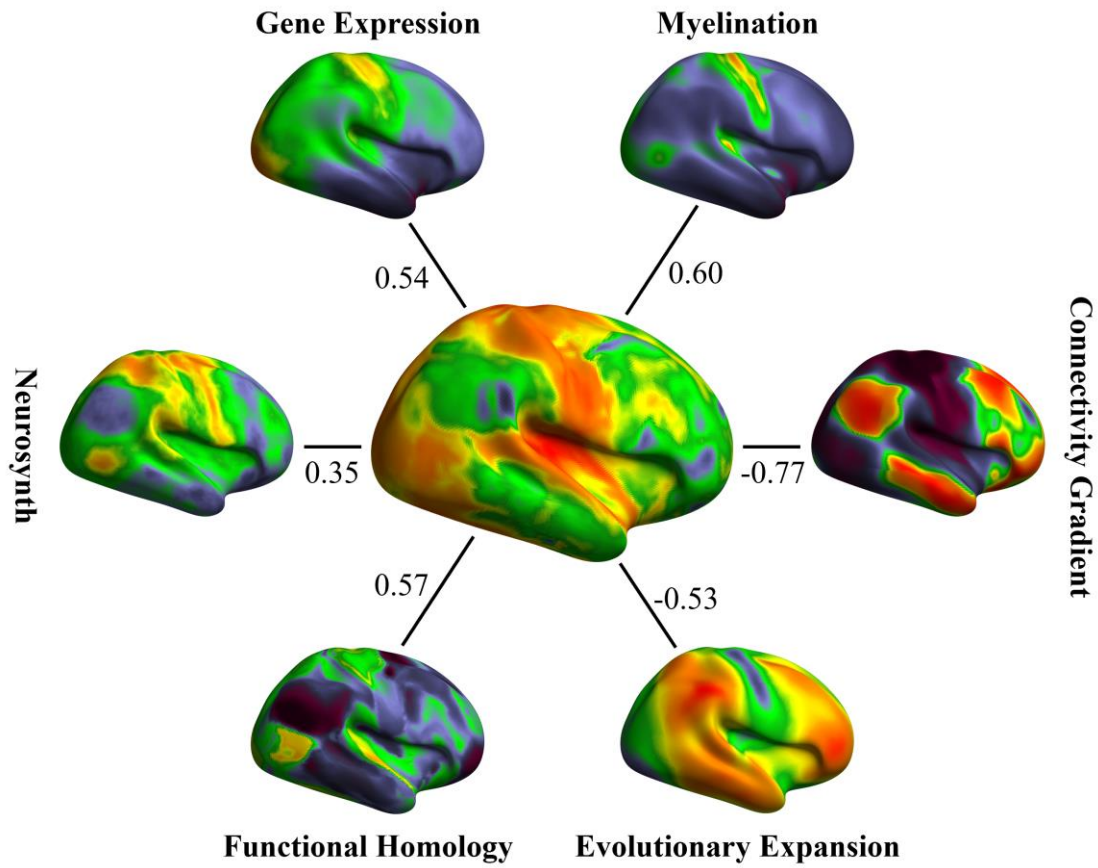

Figure 6: Multimodal Brain Atlas Correlation with the HCP Homotopic Functional Affinity Map.

Specifically, the homotopic functional affinity shows the strongest correlation with the functional connectivity principal gradient atlas (HCP: r = -0.77; CHCP: r = -0.73), with the negative correlation indicating that the higher the region's homotopic affinity, the lower its functional connectivity hierarchy, and vice versa. The cortical evolutionary expansion also shows a negative correlation with homotopic affinity (HCP: r = -0.53; CHCP: r = -0.45), suggesting that regions with strong evolutionary expansion often have lower homotopic affinity, and vice versa. The homotopic affinity shows positive correlations with the gene expression, functional homology index, and cortical myelination atlases (ranging between 0.53 and 0.60), indicating that the higher the region's homotopic affinity, the stronger its genetic, cross-

species functional homology, and cortical myelination constraints, and vice versa. Finally, the correlation coefficient between homotopic affinity and the Neurosynth cognitive activation synthesis atlas is the lowest (HCP: r = 0.35; CHCP: r = 0.38), suggesting that regions with higher homotopic affinity have more clearly defined cognitive associations, while regions with lower homotopic affinity require further exploration of cognitive associations.

3 Discussion

In this study, we introduced the method of homotopic functional affinity and validated its reliability and validity for measuring individual differences. Homotopic functional affinity serves as a reliable indicator for assessing the integration and specificity of homotopic brain regions, holding special significance in genetics, evolution, and functional organization. Utilizing this method, we revealed the functional complexity of the temporo-parietal junction, demonstrating its potential scientific value and applicative prospects in studying functional differentiation across brain regions, in correlating resting-state and task-state fMRI data, as well as in cross-cultural brain mechanism research.

3.1 Reliability of the Homotopic Functional Affinity Method

Despite the widespread application of functional magnetic resonance imaging (fMRI) in brain function studies, the reproducibility of related findings remains challenging [52, 53]. One primary reason for this low reproducibility is the insufficient reliability of selected indices in experimental designs [54]. The reliability of the global mean homotopic functional affinity atlas exceeds 0.5, with vertex-wise homotopic functional affinity generally surpassing 0.4. This reliability outperforms general resting-state functional connectivity and traditional task activation methods, approaching other highly reliable resting-state fMRI metrics [13, 14], thus establishing it as a dependable measure of brain functional homotopic integration and lateralization.

In associative cortical areas like the default mode network and frontoparietal control network, the reliability of homotopic functional affinity is generally higher and consistent across datasets, aligning with the distribution patterns of other resting-state fMRI reliability metrics [14, 55]. These cortical areas exhibit significant inter-individual variability [56] but relatively smaller intra-individual variation [57, 58], making it easier to distinguish between individuals based on their activity patterns [59]. In regions

like the central sulcus, orbitofrontal cortex, and insula, where blood oxygen level-dependent signals are constrained, the reliability of homotopic functional affinity in the Human Connectome Project (HCP) dataset tends to be higher than in the Chinese Human Connectome Project (CHCP). This discrepancy may stem from differences in scanning duration across datasets, with HCP's resting-state fMRI scanning duration being twice that of CHCP. Longer scanning durations are known to provide more stable time series, reducing the impact of random fluctuations and enhancing test-retest reliability [60, 61].

3.2 Biological Implications of the Homotopic Functional Affinity Atlas

The homotopic functional affinity atlas reveals a gradual enhancement of functional specificity along the primary-associative cortical gradient axis. This axis dominates different dimensions of human brain architecture and function [28, 62]. Our study corroborates the decisive role of this gradient axis in the intrinsic functional representation of the human brain, from the perspective of functional integration and specificity differentiation in homotopic regions. Further, multimodal brain atlas correlation analysis unveils the potential genetic, evolutionary, and cognitive significance underlying this distribution pattern of homotopic functional affinity.

During embryonic development, lateralized gene expression in the human brain is already evident [63]. In the functionally lateralized language network, gene expressions related to electrophysiology and neurotransmitter circuits also exhibit hemisphere preferences [64]. The primary cortex, appearing early in evolution, is responsible for basic sensory and perceptual functions. The homotopic functional affinity method presupposes a perfectly symmetrical homotopic brain at the evolutionary starting point. As the cerebral cortex expands through evolution, associative cortex and advanced cognitive functions gradually emerge [65]. Cortical areas that have expanded the most in evolution exhibit the strongest functional specificity [4], and cognition is closely linked to hemispheric functional specificity [8]. The lateralization in language-related and frontoparietal control regions in humans is more pronounced than in macaques [6], with the lowest functional homology between human and macaque brains in these areas [47]. These findings provide insights into the underlying regulatory mechanisms and cognitive significance of hemispheric functional specificity, validating the theoretical assumptions of the homotopic functional affinity method.

3.3 Functional Specificity of the Temporo-Parietal Junction Area

The temporo-parietal junction (TPJ) is involved in a variety of complex cognitive processes and occupies a unique position in the human brain [66]. In the macaque brain, no area has yet been found that corresponds functionally to the subregions within the TPJ [47]. The homotopic functional affinity map of the human brain keenly captures the functional uniqueness of the TPJ, revealing fine-grained functional differentiation both within its subregions and between hemispheres. Overall, the cognitive functions of the TPJ exhibit a gradual transition from executive control in the ventral aspects to social cognition, and then to language processing in the dorsal aspects [67]. In the functional network division of the right hemisphere, rTPJa and rTPJc are part of the ventral attention network and the frontoparietal control network. Meta-analyses have found significant correlations of these areas with somatic pain and vision, suggesting an inseparable link between somatosensory processing, attention orientation, and executive control [68, 69]. Rajimehr and colleagues discovered that task activation in the core language areas of the left side corresponds to the activation in social tasks on the right [70]. Meta-analyses of bilateral TPJp reiterated the functional lateralization complementarity of this region in language and social cognition, providing valuable insights into understanding the neural mechanisms of interaction and related diseases. Furthermore, the changes in activation of various TPJ subregions during language processing tasks and their association with homotopic functional affinity correspond with changes in their resting-state whole-brain functional connectivity patterns, demonstrating the enormous potential of TPJ's whole-brain functional connectivity patterns in predicting intra- and inter-hemispheric information flow during language processing.

3.4 Cultural and Ethnic Differences in the Homotopic Functional Affinity Map

This study has produced homotopic functional affinity maps of the human brain for both American and Chinese datasets with high spatiotemporal resolution. Despite the overall high similarity in patterns between the Chinese and American maps, systematic differences exist in certain brain areas. For example, the relative homotopic functional affinity of TPJc compared to TPJa and TPJp shows noticeable differences in the two datasets. The most significant differences stem from the distinct populations. The enormous cultural and ethnic differences between Chinese and American groups, which bring about differences in cognition, are likely reflected in these disparities [71, 72]. TPJc, primarily associated with social cognitive functions, shows dataset variations in homotopic functional affinity that may represent

these cultural and ethnic differences. The correlation results between cognitive task activation and homotopic functional affinity support this interpretation. During social cognition tasks, significant correlations between activation and homotopic functional affinity in the TPJ in the HCP dataset are not evident in the CHCP dataset. Moreover, under arithmetic conditions of language processing tasks, significant correlations in the CHCP dataset are not observed in the HCP dataset. Different cultural backgrounds between the East and West have been proven to be one of the factors influencing individual learning styles [73, 74]. These results provide important references for the manifestation of cultural and ethnic differences in brain function between Chinese and American populations.

4 Outlook

This paper proposes a new method of homotopic functional affinity based on the dual-factor generative theory of the connectome, illustrating its significant prospects in understanding emerging brain function mapping methods and deconstructing the psychological cognitive mechanisms of the human brain.

Methodologically, homotopic functional affinity is a subset in the process of functional connectivity gradient computation. Current research reports a high similarity between homotopic functional affinity maps and principal gradient maps. Thus, the weight of homotopic functional affinity maps in gradient calculations, their differences and similarities with principal gradient maps, and their cognitive significance remain unknown. Moreover, the calculation of homotopic functional affinity incorporates connections of each point with the whole brain. Since different regions have varying preferences for intra- and inter-hemispheric connections, the difference in affinity between hemispheric connections and within-hemisphere connections of homotopic regions is also noteworthy.

From an evolutionary and developmental perspective, the current study reveals a close correlation between homotopic functional affinity maps and human brain evolution. Whether similar maps exist in the brains of different species and whether cross-species comparisons of homotopic functional affinity maps can provide more references for human brain evolution are questions that require further investigation. In the developmental process, the homophilic factor in the dual-factor generative model becomes more pronounced while the spatial factor's restraining role diminishes [18, 19]. The homotopic functional affinity method, based on this theoretical model, raises the question of whether individual

maps follow this developmental law, which needs to be explored and validated for the biological validity of the homotopic affinity method.

Lastly, the homotopic functional affinity method has unveiled the potential influence of socio-cultural differences on the functional activities of the temporo-parietal junction area, demonstrating its capability to discern variations in brain functional activity patterns across different ethnic and cultural groups. This also prompts researchers to consider the issues of cultural adaptability in behavioral paradigms within cross-cultural studies and the necessity to develop specific paradigms addressing these issues. Future research could incorporate a broader range of cross-cultural datasets to validate the current findings, and utilize this method to uncover more brain functional representations that reflect cultural and ethnic differences.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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This preprint is a translation of a paper written in Chinese originally, and currently under review in a Chinese scientific journal. The author team leveraged ChatGPT (version 4.0) to perform the translation for the main body of the paper without any post-hoc language editing by the authors. The reason we take this way of translation is to not only achieve a high efficiency but also curious about comments from the community on how well this ChatGPT-based AI can break the language barrier to improve scientific communication and discovery.

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