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Functional divergence between the two cerebral hemispheres contributes to human fluid intelligence

Xinyu Liang[1,2*], Junhao Luo[1], Liyuan Yang[1], Deniz Vatansever[2], Elizabeth Jefferies[3], Gaolang Gong[1,4*]

1. State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China
2. The Institute of Science and Technology for Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai 200433, China
3. Department of Psychology, University of York, York YO10 5DD, United Kingdom
4. Beijing Key Laboratory of Brain Imaging and Connectomics, Beijing Normal University, Beijing 100875, China

* **Corresponding author:** Xinyu Liang, Ph.D., E-mail: xinyu_liang@fudan.edu.cn; Gaolang Gong, Ph.D., E-mail: gaolang.gong@bnu.edu.cn

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Abstract

Hemispheric lateralization is linked to potential cognitive advantages. It is considered a driving force behind the generation of human intelligence. However, establishing quantitative links between the degree of lateralization and intelligence in humans remains elusive. In this study, we propose a novel framework that utilizes the hyperaligned multidimensional representation space derived from hemispheric functional gradients to compute between-hemisphere distances within this space. Our analysis improves the functional alignment between the hemispheres, making it possible to delineate aspects of human brain lateralization that relate to individual differences in cognitive ability more precisely. Applying this framework to the Human Connectome Project (HCP) large cohort (N = 777) identified the highest functional divergence within the frontoparietal control network across the two hemispheres. We found that spatial variability in between-hemisphere functional divergence aligned with the lateralized response patterns across multiple tasks, cortical myelination and evolutionary expansion. Furthermore, both global divergence between the cerebral hemispheres and regional divergence within the multiple demand network were positively associated with fluid composite score and partially mediated the influence of brain size on individual differences in fluid intelligence. Together, these findings illuminate the profound significance of brain lateralization as a fundamental organizational principle of the human brain, providing direct evidence that hemispheric lateralization supports human fluid intelligence.

Significance Statement

A novel framework is developed to estimate between-hemisphere distance in a functional representation space derived from connectivity gradients. This framework is used in a large sample to delineate functional lateralization in humans. Our findings offer direct proof that a larger functional difference between the two hemispheres is associated with better fluid intelligence, indicating that functional lateralization is the optimal organization for cognitive processing. Importantly, our findings reveal that the functional distance between the left and right hemispheres partially mediates the impact of brain size on fluid intelligence.

Main Text

Introduction

The left and right hemispheres of the brain are not mere duplicates; structural asymmetry and functional lateralization are well demonstrated (1–4). While previous studies using functional magnetic resonance imaging (fMRI) have revealed the pivotal role of hemispheric differences in supporting various human cognitive functions (5, 6), the origin of these functional dissociations between the hemispheres remains enigmatic and controversial. A prevailing perspective posits that this divergence is rooted in evolution, and is intimately linked with the development of human intelligence (7). This view suggests that to satisfy the varying needs of different tasks in a complex world, the brain allocates functions asymmetrically across the two hemispheres to optimize processing time (8–10). This specialization not only enhances diversity in information processing but also provides the capability of advanced cognition (11–13). According to this hypothesis, a certain level of “functional divergence” between the two hemispheres could significantly contribute to human intelligence, particularly in terms of fluid components (14). Despite mounting evidence from evolutionary and comparative studies (15, 16), there is little data in the literature that directly

demonstrates a relationship between hemispheric functional divergence and fluid intelligence in humans.

Various hemispheric lateralization patterns in brain organization (5, 17, 18) have been observed in previous studies based on resting-state functional connectivity (rs-FC), which revealed that the degree of lateralization is associated with specific aspects of cognitive performance, such as language comprehension or visuospatial ability (5). These measures capture isolated aspects of functional divergence across the two hemispheres, and as such, they are insufficient for understanding the contribution of hemispheric lateralization to overall intellectual capacity. Moreover, the commonly adopted approach for comparing functional lateralization often involves using flipped or anatomically aligned hemispheres based on landmarks (5, 19). This practice could result in a misalignment of the functional organization across the hemispheres and hamper the accurate estimation of hemispheric functional divergence. Precise estimation of functional distinctions between hemispheres across the entire cortex requires not only structural alignment based on homotopical landmarks but also improved functional correspondence.

To solve these technical issues, we adopted functional alignment (i.e., hyperalignment), aiming at facilitating functional correspondence between the two hemispheres (20). In contrast to existing connectivity alignment methods (21), we integrated the hemispheric functional connectivity gradients developed in our previous work (22). We first estimated functional gradients—i.e., patterns that represent variations in connectivity space that explain the most variance—for the two hemispheres separately, revealing similar but slightly different patterns. This implies that the two hemispheres have a shared functional space, which can then serve as a representational space for functional alignment (23, 24). As a fundamental principle of organization, the cognitive relevance of functional gradients could also facilitate our investigation of fluid intelligence (25, 26).

In summary, we sought to explore the significance of between-hemisphere functional divergence for supporting human fluid intelligence. To address this issue, we used the resting-state fMRI dataset from the Human Connectome Project (HCP) (27). We examined within-hemisphere vertexwise resting-state functional connectivity profiles, identified gradients to define a common low-dimensional functional space, and then calculated the between-hemisphere functional distance across homotopic vertices after alignment to this representational space. We tested whether global or vertexwise hemispheric differences contributed to individual differences in fluid intelligence. In addition, evolutionary evidence shows that brain size plays a crucial role in both general intelligence (28–30) and functional lateralization (31–34). Hence, we considered brain size as a physical underpinning of cognition and further proposed a possible pathway in which hemispheric differences might mediate the influence of brain size on fluid intelligence. Finally, we investigated potential biological factors contributing to hemispheric functional distance.

Results

To precisely characterize the functional divergence between the two hemispheres, we propose a novel analytical framework (as shown in Fig. 1) that leverages resting-state fMRI data from 777 right-handed young adults in the HCP cohort (female/male = 428/349; age range = 22-36 years). We identified vertexwise hemispheric functional gradients for each hemisphere on the 10k cortical surface, providing a more detailed and gradual transition than in our previous work (22). Specifically, two sets of the top 10 gradients were extracted from individual left and right hemispheres (35). All individual hemispheric gradients were subsequently hyperaligned through

Procrustes rotation to a template representational space derived from the group-level left-right averaged functional connectivity (FC) profiles (Fig. S1), which maintained the internal structure of each hemisphere. The vertexwise between-hemisphere functional distance was measured as the high-dimensional Euclidean distance between each pair of homotopic cortical vertices in the representational space for each participant. The global functional divergence between the left and right hemispheric modules was evaluated by averaging vertexwise between-hemisphere functional distances across the entire cortex. We further performed dimension selection based on the balance between explained variance and test-retest reliability (Fig. S2). We calculated the intraclass correlation coefficient (ICC) of the global metrics and found that it reached a plateau when utilizing the first 6 dimensional axes (global = 0.63, vertexwise = 0.44 ± 0.19). If more dimensions were included, the dimensions with low explanatory rates also introduced more noise components. Hence, a 6-dimensional representation space, capturing 53.47% of the variance in connectivity, was employed to measure between-hemisphere functional distances across individuals. To further mitigate potential noise and reduce comparison time, both vertexwise and global between-hemisphere functional distances were averaged across two sessions for each participant in the subsequent analyses.

In addition, we estimated the correlation between the hemispheric differences within each of the top 6 gradients and the between-hemisphere functional distance (Fig. S3). The results indicated that global hemispheric differences in the principal gradient (unimodal to transmodal; $r = 0.65$, $p < 0.001$) and the tertiary gradient (default to task-positive; $r = 0.68$, $p < 0.001$) make particularly large contributions to the individual differences of global functional distance, while the secondary gradient (somatosensory to visual; $r = 0.32$, $p < 0.001$) makes the lowest contribution. The remaining gradients showed medium correlations (above 0.4) with the functional distance. Overall, this analysis suggests that between-hemisphere functional distance is an integration of multiple gradients rather than being solely driven by any single gradient.

The between-hemisphere functional divergence varies across networks

The spatial distribution of average maps of between-hemisphere functional distance across all participants was first visualized on the cortical surface (Fig. 2a). Notably, the between-hemisphere functional divergence varied widely across the cortex, with greater hemispheric divergence in transmodal regions than in primary and unimodal regions. Owing to the asymmetric distribution of Yeo's 7 networks (36), we retained only the homotopic vertices in each network that belong to the same network in both the left and right hemispheres. The networks were arranged according to the degree of hemispheric divergence in descending order from transmodal regions to unimodal regions, including the frontoparietal control network (FPN), dorsal attention network (DAN), default mode network (DMN), limbic network, ventral attention network (VAN), somatomotor network (SMN), and visual network (VN). In addition, vertices belonging to different networks across hemispheres were designated as a mismatch zone. The mismatch zone was situated at the boundaries between adjacent networks and showed a very high between-hemisphere functional distance, second only to that of the FPN. Subsequent analysis indicated that the vertices belonging

to the DMN in the left hemisphere and the vertices belonging to the FPN in the right hemisphere contributed the most to this mismatch zone (accounting for 31.76%, Fig. S4).

The spatial variability of cortical between-hemisphere functional distance reflects hemispheric functional specialization across multiple tasks

We hypothesize that functional divergence between the two hemispheres during the resting state could serve as a foundational backbone supporting segregated and lateralized functional activities across a range of functional tasks. To validate this hypothesis, we first examined whether the spatial distribution of between-hemisphere functional distance aligns with the cortical pattern of overall functional lateralization observed in meta-analytic task activations. We obtained an overall functional lateralization index for the cortical surface across multiple cognitive domains (all 575 cognitive terms) from previous studies based on the Neurosynth database (2, 37) (Fig. 2c). The significance of the spatial correspondence between the between-hemisphere functional distance derived from intrinsic connectivity and the overall functional lateralization index derived from meta-analytic task data was assessed using a spin permutation test, which generates the significance level (denoted as p_{spin}) based on a null distribution of randomly rotated brain maps that preserve the spatial covariance structure of the original data (using 10,000 permutations). Between-hemisphere functional distance was significantly correlated with the distribution of overall functional lateralization (*rho* = 0.182, p_{spin} = 0.010; Fig. 2c).

Furthermore, we conducted a topic term-based meta-analysis along the between-hemisphere functional distance map within 5-percentile bins for each hemisphere (38, 39). The resultant topic terms were sorted by their positively weighted average positions along each hemisphere, revealing a systematic shift from perception to higher-level cognition, especially cognitive control, language, number processing and working memory (Fig. 2d). Although the order of topic terms was relatively consistent across the left and right hemispheres, functions such as language, long-term memory, mentalizing and semantic categorization were found to be closer to the highest level in the left hemisphere than in the right hemisphere, whereas functions such as facial expression discrimination, visual attention and inhibition demonstrated the opposite pattern (Fig. S5).

Demographic and physiological associations with global between-hemisphere functional distance

At the individual level, we initially focused on the relationships between global between-hemisphere functional distance and demographic and physiological factors, such as age, sex, handedness and brain size, which have been associated with hemispheric functional lateralization in previous studies. Although we regressed out the parameters of in-scanner head motion during preprocessing, we still included the mean framewise displacement as a covariate in all subsequent analyses due to evidence that head motion is a confound of intrinsic connectivity metrics as well as fluid intelligence (40). For each participant, the total brain volume was calculated by summing the volumes of gray matter and white matter. For each factor, we employed partial correlation, with the other factors serving as covariates. Although the age range (22–36 years) of the adult participants was relatively narrow, the global functional distance between the two hemispheres was significantly positively correlated with age (r = 0.159, p < 0.001; Fig. S6a). In terms of sex, the global between-hemisphere functional distance in males was significantly greater than that in females ($F_{(1,749)}$ = 5.55, p = 0.019; Fig. S6b). Global between-hemisphere functional distance was also positively correlated with total brain volume (r = 0.238, p < 0.001; Fig. 3a), as larger brains showed a greater functional distance between the two hemispheres. There was no correlation

between the global between-hemisphere functional distance and handedness score (r = 0.052, p = 0.155; Fig. S6c).

The global between-hemisphere functional distance mediates the effect of brain size on fluid intelligence

We hypothesized that the overall functional divergence between the two cerebral hemispheres positively contributes to enhancing fluid cognitive capabilities. To verify this hypothesis, we explored the association between global between-hemisphere functional distance and fluid intelligence. Here, we utilized the composite score of fluid intelligence from the National Institutes of Health (NIH) Toolbox Cognition Battery (41), which combines scores on cognitive flexibility, executive inhibition, episodic memory, working memory, and processing speed. The global between-hemisphere functional distance was positively correlated with the fluid cognition composite score (r = 0.125, p < 0.001), indicating that participants with a greater hemispheric functional distance had slightly greater fluid intelligence. Given the significant relationship between total brain volume and fluid cognition (r = 0.134, p < 0.001), we additionally included brain size as a covariate. After controlling for total brain volume, the correlation between global between-hemisphere functional distance and fluid cognition was weaker but still significant (r = 0.096, p = 0.008). To further explore which cognitive domain makes the strongest contribution to this relationship, we conducted post hoc correlation analyses. Among the five subdomain scores, we only observed a significant positive correlation between cognitive flexibility and global between-hemisphere functional distance (r = 0.134 p < 0.001; Table S1).

To test our hypothetical pathway whereby hemispheric difference mediates the influence of brain size on fluid intelligence, we tested a mediation model including total brain volume as the predictor, global between-hemisphere functional distance as the mediator, and the fluid cognition composite score as the outcome (path c, β = 0.17, p < 0.001; path a, β = 0.30, p < 0.001; path b, β = 0.10, p = 0.014). Bootstrap simulation analysis (10,000 times) confirmed a significant indirect effect (a × b = 0.03, 95% confidence interval = [0.02, 0.04], p < 0.001; Fig. 3a). Our findings suggest that between-hemisphere functional divergence can partially explain the association between brain size and fluid cognitive ability.

The role of vertexwise between-hemisphere functional distance in fluid intelligence

As we identified a significant association between global between-hemisphere functional distance and the fluid composite score, we further aimed to investigate which specific brain regions are implicated in this relationship. We employed a general linear model (GLM) capturing between-hemisphere functional distance at the vertexwise level. After controlling for age, sex, handedness, head motion and brain size, we found that better fluid intelligence was associated with between-hemisphere functional distance in the inferior parietal cortex (area PFm), anterior dorsolateral frontal cortex (area a9-46v), orbital prefrontal cortex (area p47r), anterior ventral insula (area AVI), dorsal part of the lateral intraparietal region (area LIPd), and dorsal part of the ventral anterior cingulate (area 24dd) according to multimodal parcellation (42) (Fig. 3b). These regions were mainly located in the FPN or mismatch zone in Yeo's 7 networks (Fig. S7). For instance, the vertices comprising significant homotopic pairs in PFm were affiliated with distinct networks, as the left component was in the DMN, while the right component was in the FPN.

In addition, we conducted a post hoc correlation analysis on all significant vertices (179 vertices) as a combined mask. The average between-hemisphere functional distance in the combined mask

exhibited a positive association with the fluid cognition composite score (r = 0.265, p < 0.001). To test whether the average between-hemisphere functional distance in this significant mask also mediates the effect of brain size on fluid intelligence, we performed a similar mediation analysis as above. Our findings demonstrated a significant partial mediating effect of between-hemisphere functional distance on the relationship between brain size and fluid intelligence (path c, β = 0.17, p < 0.001; path a, β = 0.21, p < 0.001; path b, β = 0.27, p < 0.001; a × b = 0.06, 95% confidence interval = [0.05, 0.07], p < 0.001; Fig. 3c).

Potential biological determinants affecting between-hemisphere functional distance

We evaluated how strongly between-hemisphere functional distance was associated with cortical microstructure reflecting myelination. The cortical T1w/T2w map (Fig. 4a) has been proposed as an in vivo measure that is sensitive to regional variation in gray matter myelin content (43). We found that cortical between-hemisphere functional distance was significantly correlated with group-averaged T1w/T2w (averaged across the left and right sides, *rho* = -0.55, p_{spin} < 0.001), indicating a potential contribution of myelination to between-hemisphere distance: the most functionally divergent regions across the left and right hemisphere are also the least myelinated. In addition, we tested the hypothesis that between-hemisphere functional divergence is driven by evolutionary change. Our results indicated that the spatial pattern of between-hemisphere functional distance is well aligned with evolutionary cortical expansion indices (*rho* = 0.56, p_{spin} = 0.001), which reflect cortical expansion in humans relative to macaques (Fig. 4b) (44). Moreover, we found no significant correlation between between-hemisphere functional distance and developmental expansion (*rho* = 0.30, p_{spin} = 0.035), which is a metric that reflects cortical expansion in human adults relative to human infants (Fig. 4c). Together, our results demonstrate that between-hemisphere functional divergence is influenced by myelination and could be an evolutionary outcome suggesting that it may confer functional advantages that benefit survival and reproduction.

Validation analyses

To assess the robustness of our findings, we repeated the main analyses while regressing out the global signal of the whole brain (Fig. S8 and Table S2). Our main results were largely replicated, suggesting that our findings are reliable. In addition, to estimate the stability of the association between global between-hemisphere functional distance and fluid intelligence influenced by sample size (45), we computed sampling variability across 1000 random subsamples at a range of sampling rates (15 intervals evenly spaced from 50 to 750). The relationship becomes stable once the sample size reaches 650 (Fig. S9).

To substantiate the efficacy of our proposed framework, we also considered whether alternative measures of hemispheric functional differences would identify relationships with fluid intelligence. Specifically, we computed the homotopic FC (46) and the lateralization of within-hemisphere FC strength (17) for each pair of homotopic vertices. Homotopic FC describes the functional synchrony of time series data, while the lateralization of within-hemisphere FC strength reflects the absolute degree of hemispheric differences in functional integration within each hemisphere. Compared to between-hemisphere functional distance, homotopic FC displayed a comparable ICC across scan sessions (global = 0.68, vertexwise = 0.60 ± 0.14), whereas the ICC of lateralization of within-hemisphere FC strength was much lower (global = 0.52, vertexwise = 0.18 ± 0.07, Fig. S10). Notably, neither global metric demonstrated statistically significant correlations with the fluid cognitive composite (homotopic FC: r = -0.021, p = 0.569; lateralization of within-hemisphere FC strength: r = 0.007, p = 0.854; Table S3). This demonstrates the value of our approach based on

dimensions of intrinsic connectivity; by focusing on a small number of variables that explain the most functional variance, it is possible to discern hemispheric differences that predict individual differences in cognition.

Discussion

By leveraging state-of-the-art functional alignment and connectivity gradient techniques, we introduced a novel analytical framework to assess between-hemisphere distance in a functional representational space, which effectively quantified the level of functional divergence in each brain region and showed spatial alignment with lateralized response patterns in task meta-analysis. Our findings revealed a greater functional distance between the two hemispheres within the frontoparietal network and between mismatched pairs of vertices belonging to the left DMN and right FPN. Notably, these regions with high between-hemisphere functional distances are involved in higher-order cognitive functions, particularly cognitive control. We directly verified the association between global between-hemisphere functional distance and fluid intelligence, thereby providing the empirical evidence for the hypothesis that hemispheric specialization affords functional advantages across multiple cognitive domains in humans. Global and regional between-hemisphere functional distance also mediated the influence of brain size on fluid intelligence. Finally, we demonstrated the contribution of structural features to the spatial pattern of between-hemisphere functional distance, including the effects of cortical myelination and evolutionary area expansion. These discoveries collectively bridge a significant gap, elucidating the intricate mechanisms behind the formation of functional hemispheric lateralization to support fluid cognitive intelligence.

The cortical pattern of between-hemisphere functional divergence shows high similarity with previous hemispheric lateralization patterns observed across multiple levels of functional activity and connectivity, including meta-analytic activation (2), within-hemisphere integration (17, 47–49), between-hemisphere integration and segregation (5, 6, 18, 50) and hemispheric gradients (22–24). However, our results also provide a more holistic delineation of the complex structure of hemispheric lateralization by simultaneously considering multiple gradients that reflect the core dimensions of functional representational space; in this way, we are better able to identify the impact of lateralization on fluid intelligence. This high-dimensional space captures subtle interactions among gradients and largely avoids the methodological problems of traditional asymmetry index ([L-R]/[L+R]), such as arbitrary cut-offs that classify dominance, nonnormal distributions, and inapplicability of negative values (51, 52), to provide more accurate, sensitive and reliable estimates of brain lateralization, which can be applied in many contexts that examine functional hemispheric dissociations.

Leveraging this metric of between-hemisphere functional distance, we revealed an association between hemispheric lateralization and individual differences in fluid intelligence. This link is consistent with, and helps to unify, previous findings suggesting that specific cognitive processes are supported by lateralized patterns of functional organization, including visuospatial attention and long-term memory (5, 13, 47). These benefits to specific aspects of cognition might facilitate fluid abilities. In the two-component theory of intelligence (14), fluid intelligence is thought to be associated with metacognition and the executive control of cognitive processing to achieve adaptive cognition (53). Our vertexwise analysis revealed that lateralization in the rostrolateral prefrontal cortex (RLPFC) and the anterior extent of the inferior parietal lobule (IPL) are significantly related to fluid intelligence. These regions fall within the FPN, which is associated with the

integration of information across networks to facilitate flexible and adaptive cognition (54). Studies have shown that bipartite subsystems of the FPN differentially support distinct aspects of cognitive control (54; 55). The Control-A subsystem (including the dorsolateral prefrontal cortex) is more closely coupled with attention regions in the DAN, while the Control-B subsystem (including the IPL and the RLPFC) is more closely coupled with memory regions located in the DMN (23, 54, 55). Adaptive cognition needs to integrate controlled retrieval of meaningful information from memory with external goal-driven attention. Depending on the demands of cognitive tasks, these subsystems within the FPN may induce distinct patterns of lateralization. For example, the control of semantic cognition as well as internal states could involve a more leftward asymmetric pattern of network coupling than the control of spatial attention (23). We speculate that these segregated patterns of connectivity for control subsystems across hemispheres could give rise to functional benefits such as reduced interference and shorter network restructuring time.

Our findings extend key theoretical accounts of human fluid intelligence. The identified regions, including RLPFC and IPL, are largely consistent with the theoretical networks that underpin human intelligence. The parieto-frontal integration theory (P-FIT) proposed by Jung and Haier (56), suggests that a lateralized distributed network, including the dorsolateral prefrontal cortex and superior and inferior parietal lobule, integrates knowledge to support reasoning and problem solving. Similarly, the multiple demand (MD) system located in the prefrontal and parietal cortex has been suggested to be a key network supporting fluid intelligence (57). The MD system is typically assumed to be bilateral due to the methodology used to identify this network, which relies on shared activation patterns across a wide range of tasks (58); these tasks may manifest varying degrees of lateralization but become symmetrized after averaging across different activation patterns. Our discoveries extend these theories by showing that frontoparietal systems can be asymmetrically active and that between-hemisphere functional divergence acts to support fluid intelligence.

The positive association of brain size with general intelligence has been validated in multiple in vivo human studies, including meta-analyses ($r = 0.24$, $N = 8{,}036$ from 148 independent samples) (29), and in large cohorts including the HCP ($r = 0.24$, $N = 896$) (30) and the UK Biobank ($r = 0.28$, $N = 7{,}201$)(28). Despite the robustness of this association, the reasons why and how brain size could affect human intelligence are still debated (29). Moreover, many studies have shown a relationship between whole-brain size and brain lateralization (31, 32, 59). This relationship can be traced back to evolutionary theories about the formation of functional lateralization (9, 60, 61). Our findings provide vital evidence extending this hypothesis to humans, suggesting that divergent functions across hemispheres are beneficial for human fluid intelligence, especially for people who have larger brains. This may be a consequence of both a reduction in the time-consuming transmission of information and the prevention of interference between the hemispheres, maximizing the efficiency of neural processing.

Our findings also revealed that prominent between-hemisphere divergence is located in regions linked to dramatic cortical expansion during evolution (62). Evolutionary cortical expansion has been implicated in human cognitive capacities, such as language (63). Our results further suggest that evolutionary cortical expansion, rather than developmental processes, plays a considerable role in shaping the spatial distribution of functional lateralization across the entire cortex. The significant association between cortical myelination and between-hemisphere divergence is also

compatible with the idea that more lateralized regions have a smaller density of interhemispheric connections (2, 64).

There are, of course, potential limitations of this study. First, due to the high computational cost of extracting vertexwise gradients, it was not feasible to replicate the results fully in another large dataset. Future work can optimize the balance between spatial resolution and computational cost to make our analysis approach more efficient. Second, structural white matter connections are likely to be relevant to between-hemisphere functional distance, and further research is needed to explore this relationship. Third, we confined our analyses to healthy young right-handed adults and one should be cautious when generalizing our conclusions to left-/bilateral-handed adults, children or elderly individuals. Finally, the lifespan trajectory of between-hemisphere functional distance warrants future investigation to reveal its development.

In conclusion, this study highlights the significant contribution of between-hemisphere functional lateralization to human intelligence, and the method we developed could serve as a catalyst for the continued exploration of the origins and significance of brain lateralization.

Materials and Methods

The participants in the present study were from the HCP S1200 release (27). The HCP was reviewed and approved by the Institutional Ethics Committee of Washington University in St. Louis, Missouri. All participants gave written informed consent. For more details, please refer to Van Essen et al. 2013. The final sample included 777 right-handed young adults (female/male = 428/349; age range = 22-36 years; handedness [mean ± SD] = 79.55 ± 17.85).

Using preprocessed rs-fMRI images, we estimated hemispheric functional gradients following our previous work (22). Rather than focusing on the region level, we used the vertexwise connectivity in this study to obtain a high-resolution delineation. The resultant functional gradients can be seen as a collection of continuous axes as a low-dimensional representation of the initial high-dimensional connectivity space. To ensure the comparability of the representational spaces between the left and right hemispheres, as well as across participants, we generated a group-level hemispheric gradient template for subsequent functional alignment (20). To keep the internal structure of each hemisphere unchanged, Procrustes rotation was utilized to align each hemisphere of each individual to the group-level template (65). The between-hemisphere functional distance was measured as the Euclidean distance between each pair of homotopic vertices in the first 6-dimensional common representation space defined by the template gradients. The global between-hemisphere functional distance was computed by averaging vertexwise values across the entire hemispheric cortex. The between-hemisphere functional distances were further averaged across two sessions for each participant to reduce potential noise as well as comparison time.

To assess the spatial alignment to previously characterized cortical maps, we employed the Spearman correlation coefficient (*rho*), which tested the association of between-hemisphere functional distance maps with the following public or homemade atlases: 1) the overall functional lateralization index across cognitive domains (2), 2) the evolutionary and developmental cortical expansion maps estimated by Hill and colleagues (44), and 3) the myelin (T1w/T2w) maps (66). The significance of the alignment was determined using a spatial spin test with 10,000 permutations (denoted as p_{spin}). Additionally, we conducted topic based meta-analytic functional decoding utilizing the Neurosynth database (38). Specifically, the group-averaged cortical between-

hemisphere functional distance map was divided into increments of five percentiles and converted into binary form for input into the meta-analysis. The feature terms used in this study were derived from the 50 sets of topic terms (67), and 24 topic terms related to cognitive functions were manully selected following a previous study (38).

After removing participants lacking cognitive scores or identified as outliers, a total of 755 participants were included in subsequent statistical analyses focused on individual differences. We used a partial correlation to assess the association between global between-hemisphere functional distance and fluid cognition composite score, which combines scores on the dimensional change card sort for executive cognitive flexibility, the Flanker task for executive inhibition, the picture sequence memory task for episodic memory, the list sorting task for working memory, and the Salthouse pattern comparison task for processing speed (43). In addition, a general linear model (GLM) was applied on each vertex to localize the brain regions that positively contributed to the fluid cognition composite score. To correct the multiple vertexwise comparisons, the cortical vertices with false discovery rate (FDR)-corrected $p < 0.05$ were considered as significant. To determine whether between-hemisphere functional distance could play a mediating role in the effect of brain size on fluid intelligence, we conducted a mediation analysis and tested the significance of the mediation model by bootstrapping testing with 10,000 replacements (68).
See the *SI Materials and Methods* section of the *SI Appendix* for further details.

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Figures and Tables

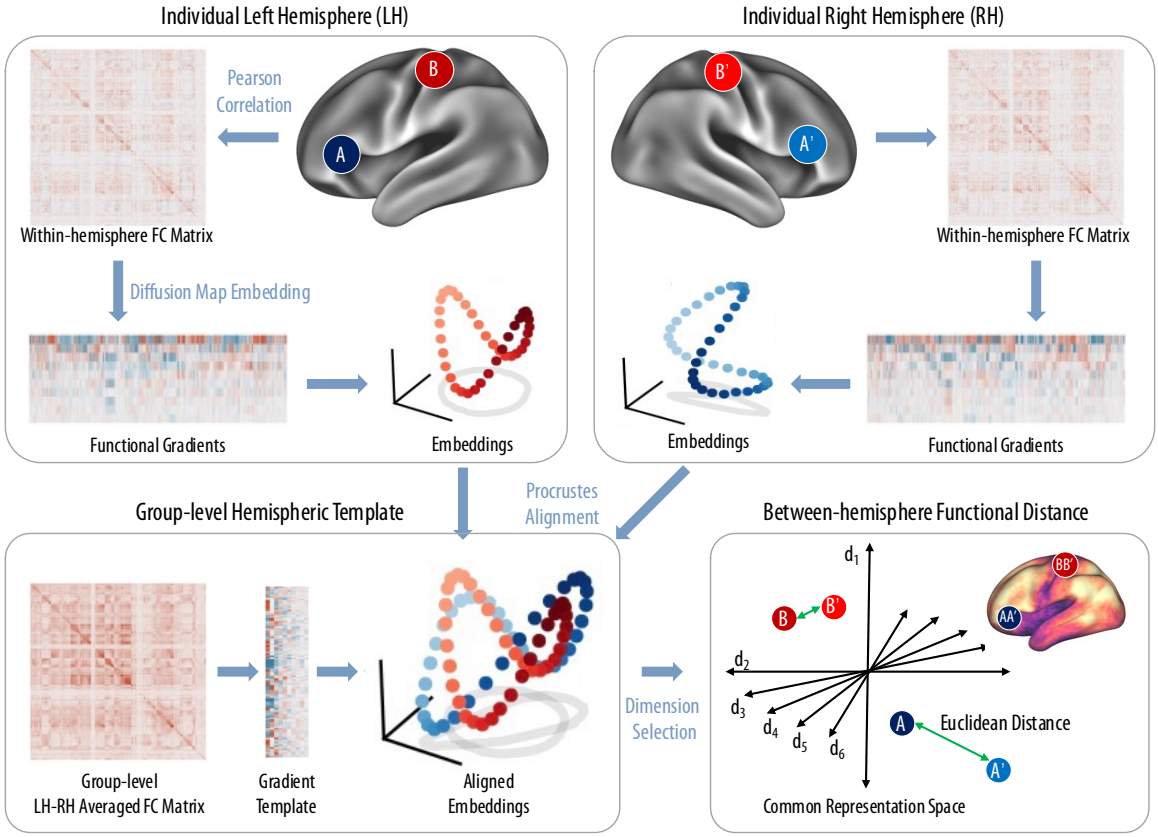

Figure 1. Framework for the computation of between-hemisphere functional distance in a common representational space. To compute between-hemisphere functional divergence, we first calculated functional connectivity (FC) between vertices within each hemisphere based on vertexwise time series data. This yielded hemisphere-specific FC matrices for each hemisphere, resulting in a 9354x9354 matrix after excluding the medial wall. Then we applied the diffusion map embedding method on hemispheric FC matrices to obtain the top 10 functional gradients. These gradients form a low-dimensional representation of the original functional connectivity space, in which the distance represents the functional similarity between vertices. To ensure better comparability between homotopic vertices within the representational spaces of the left and right hemispheres, we employed functional alignment which brought the individual left and right hemisphere embeddings into a group-level common functional space. To determine the optimal dimension for characterizing distance, we used a dimension selection process that balanced explained variance and test-retest reliability. The final between-hemisphere functional divergence was measured as the Euclidean distance between each pair of homotopic vertices in a 6-dimensional common representational space. The sketch plots of embeddings are modified from ref. 65, under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

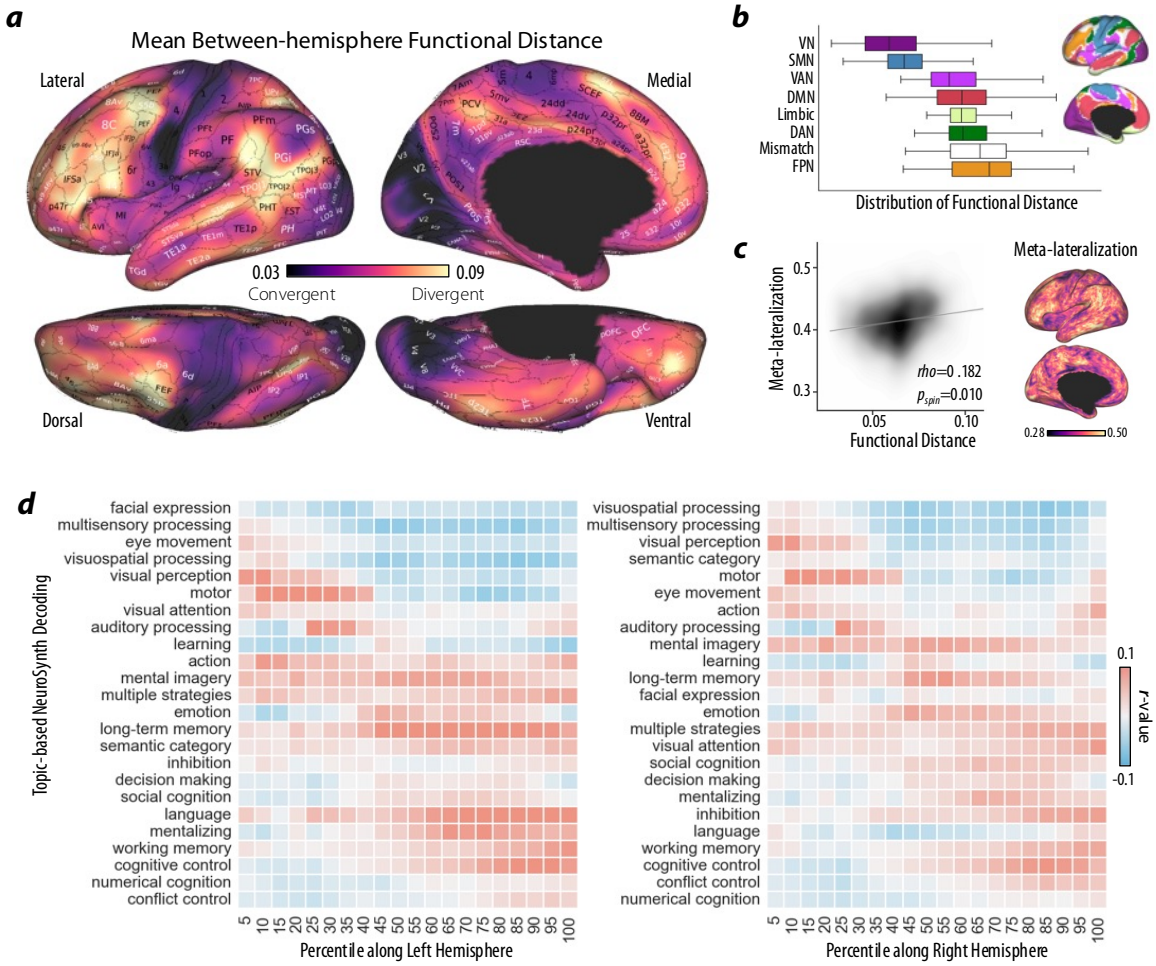

Figure 2. The cortical variation of between-hemisphere functional distance. (a). The group average map of between-hemisphere functional distance in the HCP datasets (N = 777). (b). We plotted the distribution of between-hemisphere functional distances within each network in a symmetric version of Yeo's 7 networks. The mismatch zone is defined by mismatch vertices that belong to distinct networks across two hemispheres. (c). We calculated the cortical map of the overall functional lateralization index across all 575 cognitive terms. A significant correlation between the cortical map of overall functional lateralization and the between-hemisphere functional distance map was found by a spin test with 10,000 permutations. (d). Then we used Neurosynth's ROI association approach of regions of interest along the between-hemisphere functional distance map with 24 topic terms. The terms were ordered by the positively weighted mean of their location along the left and right hemisphere.

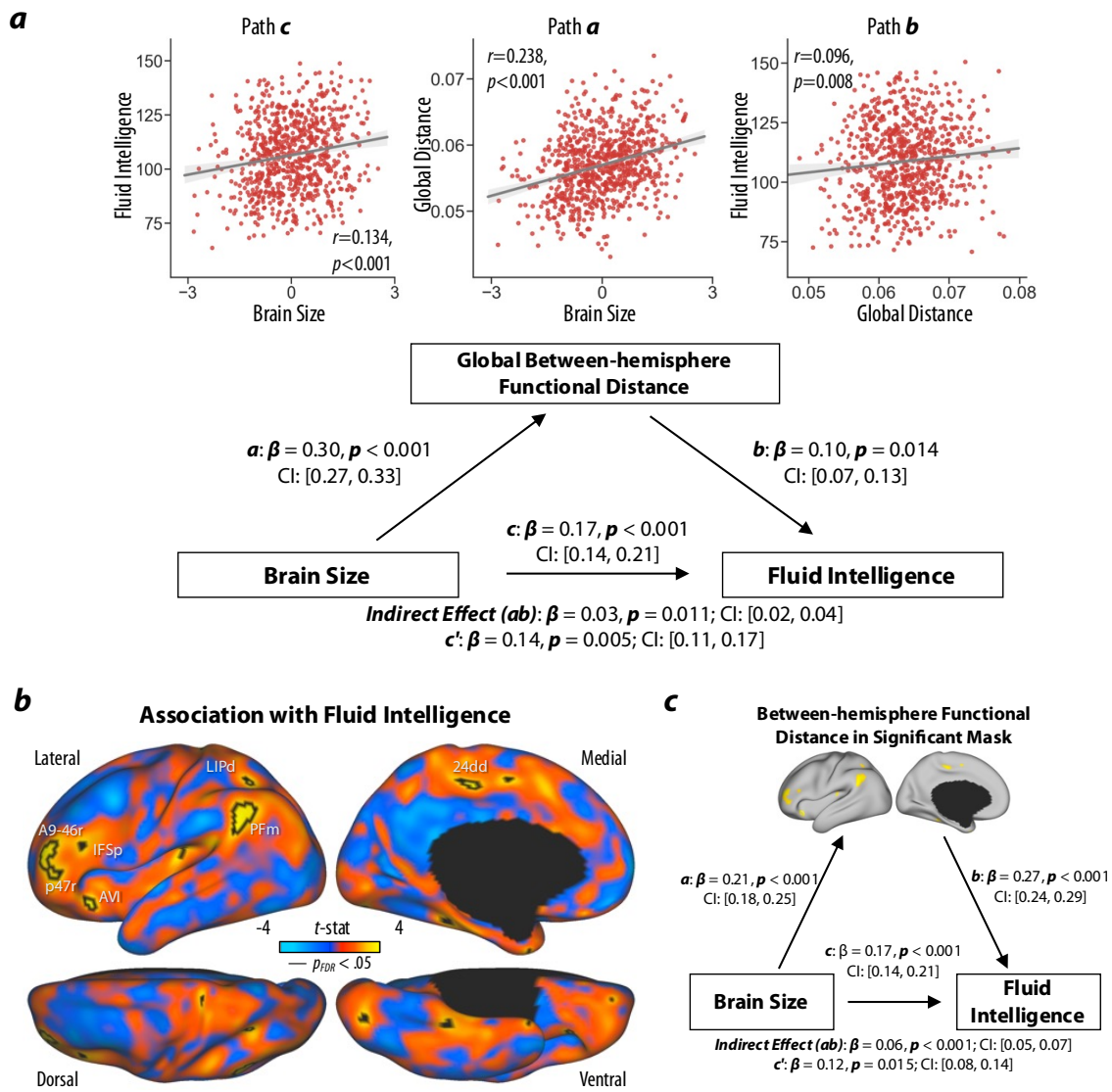

Figure 3. Individual differences in between-hemisphere functional distance mediate the effect of brain size on fluid intelligence. (a). We observed significant correlations between brain size, global between-hemisphere functional distance and fluid intelligence after controlling for age, sex, handedness and mean framewise displacement. We tested the significance of the hypothetical mediation pathway, in which global between-hemisphere functional distance could partially mediate the impact of brain size on fluid intelligence. Significance was tested by bootstrapping (10,000 replacements). (b). A GLM analysis was performed on vertexwise between-hemisphere functional distances to identify regions associated with intelligence, in which age, sex, handedness, brain size and mean FD were included as covariates. The resultant *t* maps for fluid intelligence are shown. The regions with gray outlines were significant vertices after FDR correction (one-tailed p_{FDR} < 0.05). (c). The mean between-hemisphere functional distances within a mask consists of all significant vertices also exhibited a significant mediating effect on the relationship between brain size and fluid intelligence.

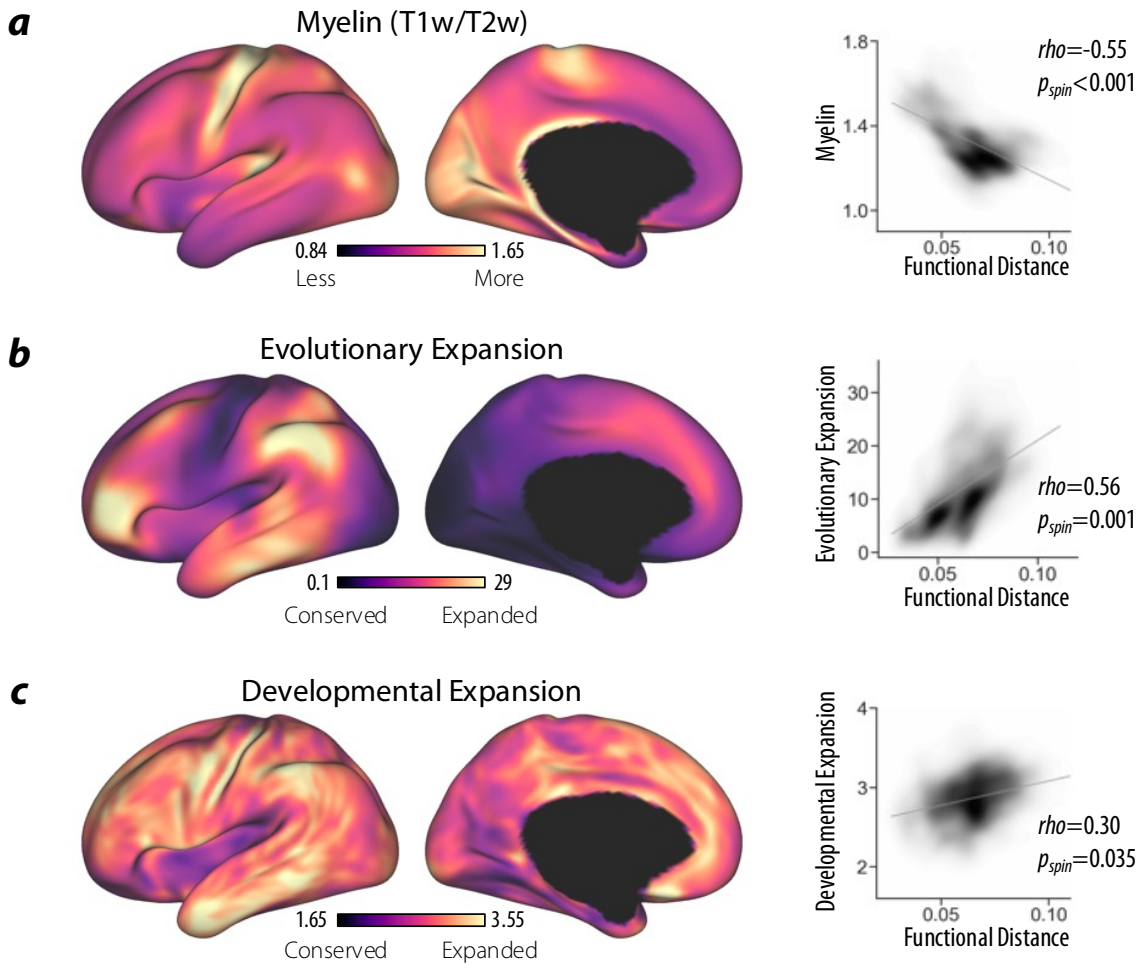

Figure 4. Spatial variability in between-hemisphere functional distance relates to biological maps. Cortical maps of myelin (a), evolutionary expansion (b), and developmental expansion (c) were utilized to test the potential biological basis for between-hemisphere functional distance. Their spatial correspondences with group-averaged between-hemisphere functional distances are plotted. The significance level was determined by a spin test with 10,000 permutations with the Bonferroni correction (p_{spin}<0.0125).