Trends in
Cognitive Sciences

CellPress

Forum

Global brain asymmetry

Yi Pu[1,*], Clyde Francks[2,3,4], and Xiang-Zhen Kong[5,6,7,*]

Lateralization is a defining characteristic of the human brain, often studied through localized approaches that focus on interhemispheric differences between homologous pairs of regions. It is also important to emphasize an integrative perspective of global brain asymmetry, in which hemispheric differences are understood through global patterns across the entire brain.

Localized approaches versus a global perspective

Functional lateralization, the specialization of cognitive and motor functions within one hemisphere, is a hallmark of human brain organization [1]. Understanding the structural basis of this lateralization is a fundamental, yet unsolved, question in cognitive and systems neuroscience. Studies on this topic have often focused on directly comparing specific brain regions with their homologous counterparts in the opposite hemisphere (Figure 1A), aiming to identify structural asymmetries associated with lateralized functions and behaviors. While these studies have revealed asymmetries in various brain regions (e.g., the leftward asymmetry of the planum temporale) [1], these structural hemispheric differences often fail to account for pronounced functional lateralization observed in many cognitive tasks [2,3]. Moreover, some of the structural asymmetries reported in these studies have not been consistently replicated [4]. These challenges highlight the need to rethink current approaches to understanding the relationship between structural asymmetries and functional lateralization in the brain.

Over the past decade, there has been a growing shift toward examining brain organization as a whole, rather than focusing solely on individual cortical areas [5]. This perspective shift is driven by the evidence that brain regions are not isolated islands, but are instead integrated into interconnected networks or continuous **gradients** (see Glossary) [5]. By concentrating only on individual areas, we risk overlooking important aspects of a bigger picture. To complement studies using localized approaches, we emphasize focusing on global patterns that may underlie localized differences, a perspective that we term 'global brain asymmetry'. Here, we provide an overview of recent evidence supporting this holistic perspective and discuss its potential to advance our understanding of the lateralized organization of the brain.

Evidence supporting the perspective of global brain asymmetry

The investigation of global patterns of brain asymmetry can be traced back to early observations of an overall twist in brain shape [6], which was termed 'torque' in subsequent literature [1]. Originally identified in postmortem studies, brain torque is recognized as a fundamental feature of brain asymmetry (see [3,7] for further discussion). Recent large-scale studies using advanced morphometric techniques revealed a consistent pattern of regional cortical thickness asymmetry along the anterior–posterior axis, which aligns with brain torque [2,8]. This intriguing pattern exemplifies the broader phenomenon of global brain asymmetry. Moreover, morphometric analyses have shown that different groups of localized structural asymmetry can be linked to certain contributing factors in common, such as shared aging-related thinning processes [9] and particular genetic variants [8]. These findings suggest the presence of multiple latent asymmetry patterns beyond brain torque, likely governed by relatively global developmental and aging mechanisms.

Recent advances in data science, particularly the availability of large neuroimaging data sets, and multivariate machine learning techniques, have made it increasingly feasible to explore the intricate details of global brain asymmetry (Figure 1B). These advances are especially helpful in two key areas: uncovering the independent components of brain asymmetry and identifying hemisphere-specific patterns.

Glossary

Asymmetry index: often calculated as the difference between the values of a specific metric (e.g., volume or thickness) in the left and right sides, divided by their average.

ENIGMA Laterality Working Group: collaborative research initiative within the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium, aiming to uncover how brain asymmetries relate to various cognitive functions and brain-related disorders.

Ensemble machine learning: machine learning technique in which multiple models are combined to improve overall performance and accuracy.

Genetic correlation: relationship between genetic influences on two traits, indicating how much the same genetic factors contribute to both traits.

Genome-wide association study (GWAS): research method that scans the entire genome of many individuals to identify genetic variants linked to specific traits or diseases.

Gradient: gradual and continuous change in a particular property or feature across the brain.

Horizontal/vertical skew: measure of asymmetry in the structure of the brain, where the left and right hemispheres exhibit different shapes or positions along the horizontal/vertical axis.

Laplace–Beltrami operator: generalization of the Laplacian that can analyze the geometry of the cortical surface at different spatial frequencies, allowing for the decomposition of cortical shapes.

Supervised machine learning: machine learning approach involving training an algorithm on a labeled data set, where each input comes with a known output.

Unsupervised machine learning: machine learning method where the algorithm learns from data without labeled outputs or explicit instructions on what to look for.

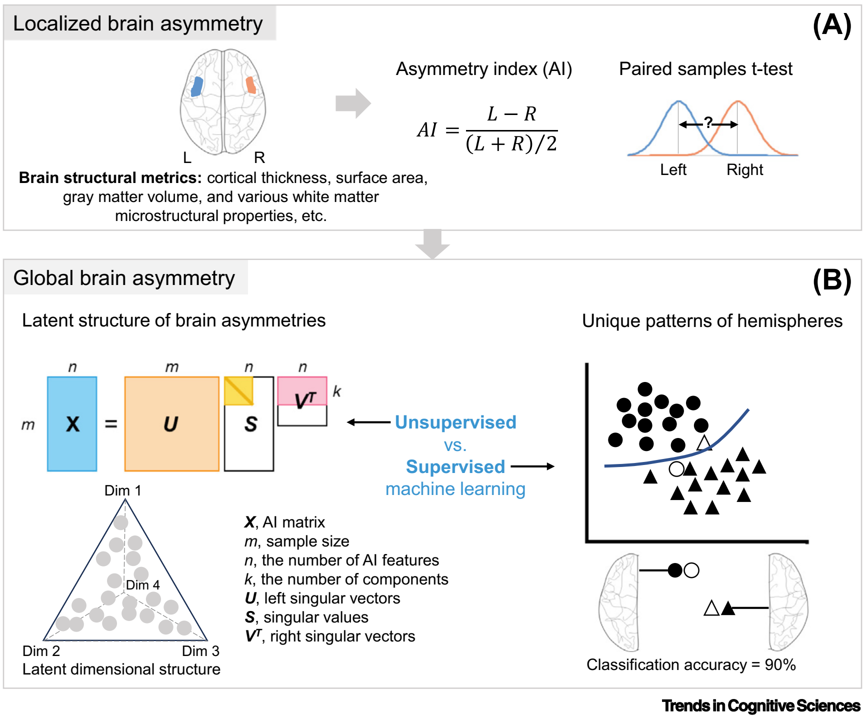

Figure 1. From localized approaches to global brain asymmetry. (A) Localized brain asymmetry is typically assessed by calculating an asymmetry index (AI) or by directly comparing left (L) and right (R) measurements (e.g., cortical thickness or surface area) using statistical methods, such as paired sample *t*-tests. This localized approach focuses on hemispheric differences of individual homologous areas (e.g., the brain areas in blue and orange). However, by concentrating solely on specific regions, broader patterns may be overlooked. To address this limitation, we emphasize a complementary perspective concentrating on 'global brain asymmetry', which is focused on patterns that transcend localized differences. (B) Global brain asymmetry involves two key concepts: the latent structure of brain asymmetries and hemisphere-specific patterns. The latent structure refers to the decomposition of multiple regional asymmetries (X) into a smaller number of components using unsupervised techniques, such as singular value decomposition (SVD) and K-means clustering. The figure shows the SVD process, including its outputs (U, S, and V), which represent a latent dimensional structure. These independent components can serve as valuable phenotypes for exploring relationships between brain asymmetries and functions, as well as for identifying underlying genetic factors. By contrast, hemisphere-specific patterns can be investigated through supervised methods, such as support vector machine (SVM) or random forest, which aim to classify the two hemispheres. The classification accuracy and identified patterns may change with healthy development, aging, or in the presence of brain disorders.

First, the latent components can be examined through the covariance of different regional asymmetries. In this context, **unsupervised machine learning** approaches are used to decompose various brain asymmetries into statistically independent components. In a recent study, researchers applied singular value decomposition to **asymmetry index** measures of 85 brain regions from over 37 000 participants and revealed multiple dissociable global asymmetry patterns, each showing specific phenotypic associations [10]. Notably, one of these derived patterns aligned with the pattern of brain torque. Additionally, researchers introduced the shape asymmetry signature based on the eigen decomposition of the cortical surface of the individual using the **Laplace–Beltrami operator**, providing a summary measure of multiscale cortical shape asymmetries [11].

Second, **supervised machine learning** models can be trained to explicitly classify the two hemispheres, thereby identifying hemisphere-specific patterns. Recent work used an **ensemble machine learning** approach to train predictive models based on morphological measures, including cortical thickness and volume, to classify the two hemispheres. As anticipated, the obtained models demonstrated high performance (90%) [12], suggesting distinct structural characteristics of the two hemispheres. These findings are in line with another study that applied a support vector machine approach focusing on volumetric differences between the hemispheres [13].

Collectively, brain asymmetry is present on a global scale. From a holistic perspective, the emerging findings reviewed earlier have revealed substantial differences between the two hemispheres, providing encouraging evidence for the potential of global brain asymmetry in understanding human brain organization.

A new window into brain laterization

A multivariate view of global brain asymmetry opens a new window for exploring how our brain hemispheres are organized, and raises many important questions for future investigation (Box 1). These include its associations with lateralized functions and behaviors, its genetic and developmental contributions, and its potential as a biomarker for assessing and diagnosing related brain disorders. Although this field is still emerging, existing data suggest that investigating global brain asymmetry holds significant promise in these areas.

For example, handedness is a prominent form of behavioral lateralization in humans, where variation may correspond with differences in brain structure. However, studies using region-based approaches have generally failed to find consistent brain-handedness associations [2]. Recently, researchers used a transformation-based approach and derived two global measures of anatomical skewing: **horizontal**

Box 1. Outstanding research questions

Regarding the latent structure of human brain asymmetries

- What is the latent structure of brain asymmetries across different imaging modalities?
- How are brain asymmetries associated with lateralized functions?
- What are the developmental trajectories of brain asymmetries?
- What are the genetic correlates of brain asymmetries?
- What are the associations of brain asymmetries with various brain disorders?

For distinct patterns of the two hemispheres

- How accurately can the hemispheres be classified?
- What features drive hemisphere-specific patterns in structure?
- What are the functional correlates of hemisphere-specific patterns in structure?
- How does classification accuracy and/or hemispheric pattern vary with age?
- How does classification accuracy and/or hemispheric pattern vary across brain disorders?

skew and **vertical skew**. Both measures showed replicable associations with handedness [3]. Moreover, these global measures were significantly associated with cognitive functions, including fluid intelligence and prospective memory [3], and the horizontal skew pattern aligned with features of brain torque. These results suggested that the latent components of global brain asymmetry are linked with different lateralized functions, warranting further investigation.

Moreover, previous studies have also suggested potential links between global patterns of structural asymmetry and brain dysfunction. For instance, the **ENIGMA Laterality Working Group** identified subtle but widespread alterations of cortical regional asymmetries in patients with various brain disorders, such as autism spectrum disorder [2]. There is also evidence of alterations in brain torque in brain disorders, including developmental stuttering, dyslexia, and schizophrenia, although these studies were limited with small sample sizes and require replication [3]. These findings suggest that global brain asymmetry reflects optimal brain functioning, with multivariate deviations from typical patterns potentially contributing to predictive models for brain dysfunction. Notably, a significant **genetic correlation** between horizontal skew and autism spectrum disorder has been observed, suggesting an overlap of associated genetic variants [3]. Similarly, a multivariate **genome-wide association study (GWAS)** of localized brain asymmetries identified shared genetic variants between brain asymmetry and autism spectrum disorder, educational attainment, and schizophrenia [8].

These emerging data provide a clear motivation for studying global brain asymmetry. As this field develops, it will be crucial to map the latent structure of global asymmetry, validate these initial findings, and explore their full implications for cognitive and systems neuroscience and clinical practice. Additionally, because some components of global brain asymmetry can be statistically independent, they can serve as valuable phenotypes for identifying genetic factors that contribute to the development of brain lateralization and related cognitive functions.

Concluding remarks

In conclusion, a multivariate approach to global brain asymmetry offers a promising perspective for understanding brain lateralization. By focusing on multiregion patterns of hemispheric differences, and incorporating machine learning techniques, this approach can offer a comprehensive view of how the left and right hemispheres are differently organized, and how deviations from typical patterns might contribute to brain disorders. These efforts represent an important step toward a deeper understanding of the organizational principles of the human brain.

Acknowledgments

The writing of this article was supported by the STI 2030-Major Projects (2021ZD0200409), National Natural Science Foundation of China (32171031, 32400882), and Information Technology Center of Zhejiang University. C.F. is funded by the Max Planck Society (Germany).

Declaration of interests

The authors declare no conflicts of interest.

[1]Shanghai Key Laboratory of Brain Functional Genomics (Ministry of Education), School of Psychology and Cognitive Science, East China Normal University, Shanghai, China
[2]Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands
[3]Donders Institute for Brain, Cognition, and Behaviour, Radboud University, Nijmegen, The Netherlands
[4]Department of Cognitive Neuroscience, Radboud University Medical Center, Nijmegen, The Netherlands
[5]Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou, China
[6]The State Key Lab of Brain-Machine Intelligence, Zhejiang University, Hangzhou, China
[7]Department of Psychiatry of Sir Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

*Correspondence:
ypu@psy.ecnu.edu.cn (Y. Pu) and
xiangzhen.kong@zju.edu.cn (X.-Z. Kong).

https://doi.org/10.1016/j.tics.2024.10.008

References

1. Toga, A.W. and Thompson, P.M. (2003) Mapping brain asymmetry. *Nat. Rev. Neurosci.* 4, 37–48
2. Kong, X.Z. *et al.* (2022) Mapping brain asymmetry in health and disease through the ENIGMA consortium. *Hum. Brain Mapp.* 43, 167–181
3. Kong, X.Z. *et al.* (2021) Large-scale phenomic and genomic analysis of brain asymmetrical skew. *Cereb. Cortex* 31, 4151–4168
4. Kong, X.Z. *et al.* (2022) Reproducibility in the absence of selective reporting: An illustration from large-scale brain asymmetry research. *Hum. Brain Mapp.* 43, 244–254
5. Bijsterbosch, J. *et al.* (2020) Challenges and future directions for representations of functional brain organization. *Nat. Neurosci.* 23, 1484–1495
6. Hadžiselimović, H. and Ruždić, N. (1966) Appearance of the base of the brain in relation to the configuration of human skull. *Cells Tissues Organs* 65, 146–156
7. Zhao, L. *et al.* (2022) Mapping complex brain torque components and their genetic architecture and phenomic associations in 24,112 individuals. *Biol. Psychiatry* 91, 753–768
8. Sha, Z. *et al.* (2021) The genetic architecture of structural left–right asymmetry of the human brain. *Nat. Hum. Behav.* 5, 1226–1239

9. Roe, J.M. *et al.* (2021) Asymmetric thinning of the cerebral cortex across the adult lifespan is accelerated in Alzheimer's disease. *Nat. Commun.* 12, 721
10. Saltoun, K. *et al.* (2023) Dissociable brain structural asymmetry patterns reveal unique phenome-wide profiles. *Nat. Hum. Behav.* 7, 251–268
11. Chen, Y.C. *et al.* (2022) The individuality of shape asymmetries of the human cerebral cortex. *Elife* 11, e75056
12. Hu, H. *et al.* (2024) Global brain asymmetry and its variations in aging and related diseases. *bioRxiv*, Published online August 30, 2024. https://doi.org/10.1101/2024.08.29.610247
13. Friedrich, P. *et al.* (2022) Is it left or is it right? A classification approach for investigating hemispheric differences in low and high dimensionality. *Brain Struct. Funct.* 227, 425–440