# Evolution of functional sulcal anatomy in primates

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## Abstract

This chapter explores how cortical folding contributes to brain function and evolution in primates. Sulci, historically considered incidental features of the cortex, are now recognized as integral to neural organization, with primary sulci systematically aligning with sensorimotor representations and tertiary sulci emerging in association cortices alongside higher-order cognitive functions. By examining cross-species comparisons, developmental mechanisms, and clinical outcomes, we highlight how genetic, cellular, and mechanical processes drive sulcal patterns in primates. We argue that sulci are a key organizational framework that structures neural processing, thereby governing the behavioral repertoires of diverse primate species.

Keywords: Brain connectivity; Comparative neuroscience; Cortical folding; Cortical function; Gyrification; Mechanical tension; Neurodevelopment; Primate brain evolution; Sulci; Tertiary sulci

Key points

- Historical Shift: Classically, often considered as random “wrinkles,” sulci now often emerge as reliable markers of cortical areas, networks, and individual differences in cognition.
- Sensorimotor Specialization: Large and deep, early emerging primary sulci align with sensory and motor maps.
- Association Cortex Specialization: Small and shallow, late emerging putative tertiary sulci align with functional areas and networks underlying higher-level aspects of cognition (language, executive function, reading, face perception).
- Evolutionary Insights: Cross-species data reveal how new folds (putative tertiary sulci) emerge alongside advanced behaviors, especially in humans.
- Mechanisms of Folding: Mechanical constraints, cellular dynamics (oRGs), and specific human genes interact with regional variations in cortical thickness, neuronal density, and axonal tension to shape sulcal patterns.
- Clinical Relevance: Sulcal patterns predict individual cognitive differences and serve as “corridors” for neurosurgery, enabling personalized interventions.

## 1 Introduction

Primates exhibit remarkable diversity in brain morphology, particularly in the extent of cortical gyrification, the formation of folds and fissures (gyri and sulci) that significantly increase the cortical surface area. While most primates possess gyrencephalic brains, the degree of folding varies widely across species, with humans displaying the most extensive convolutions. This variation suggests that gyrification has been a pivotal factor in the functional evolution of primates, enabling larger neuronal populations and new cortical networks, which together allow for more complex neural processing.

Historically, anatomists largely regarded cortical folds as mere byproducts of brain growth, serving primarily to fit a larger cortex within the limited volume of the skull. Indeed, early neurophysiologists and neuroanatomists, such as Korbinian Brodmann, focused on cytoarchitectural features to map functional areas, often overlooking the significance of sulcal patterns. Ironically, Brodmann did not systematically map cytoarchitecture within sulci despite the fact that 60–70% of the human cerebral cortex is buried in sulci (**Abbott, 2003**). **Bailey et al. (1950)** specifically pointed fingers at Brodmann and other neuroanatomists between 1905 and 1915 for this “devaluation” of sulci, writing:

> “About the turn of the century the advent of cortical cytoarchitecture tended to devalue the gross configuration of the cortex, particularly when **Brodmann (1906)** and **Ariens-Kappers (1913)** practically denied a correlation between sulci and cortical areas. Hence, we possess comparatively few modern studies of cerebral sulci”. (**Bailey et al., 1950**, p. 15).

This perspective prevailed throughout much of the 20th century, with skepticism if/how sulci had functional meaning. Consequently, theories of brain function emphasized localization based on histological criteria rather than the intricate folding patterns of the cortex. For example, primary sensory areas align with sulci in gyrencephalic brains, but are also identifiable in smooth, lissencephalic brains (**Fig. 1**), begging the question: Do sulci matter for brain function? Throughout this chapter, we will argue that sulci play a crucial role in brain

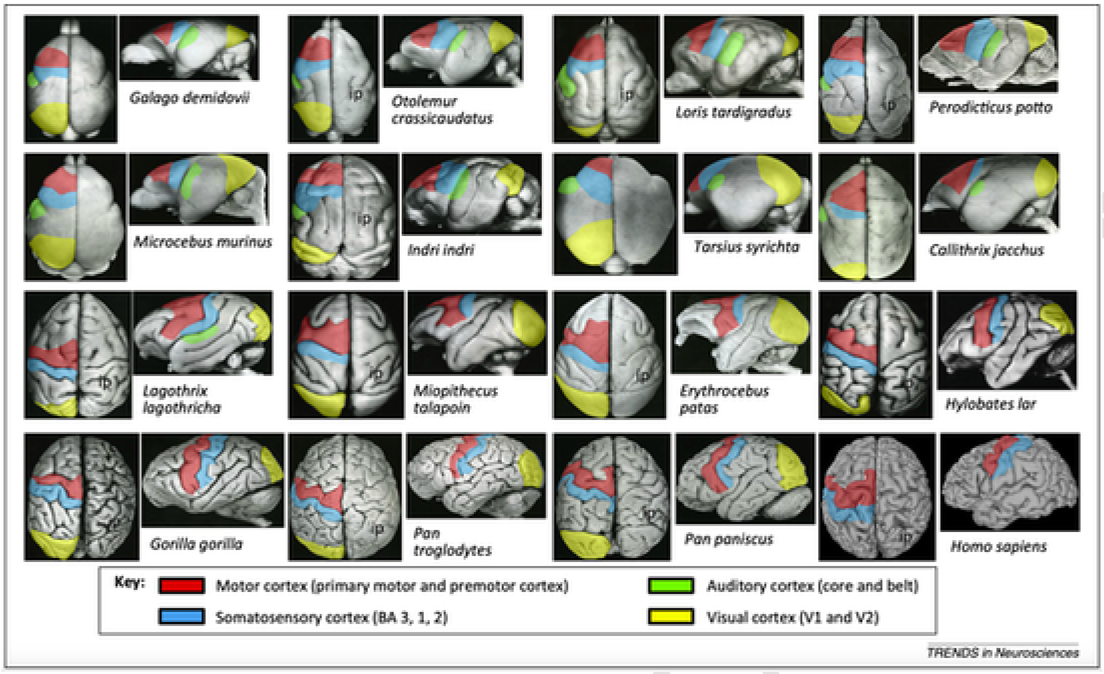

**Fig. 1** Cortical Anchors for Sensorimotor Maps Across Primates. Axial (left) and sagittal (right) views highlight how cortical folds reliably anchor motor, somatosensory, auditory, and visual processing regions across primates, regardless of cortical folding complexity. This correspondence is observed in both gyrencephalic and lissencephalic brains, emphasizing the conserved organization of sensorimotor processing. Image reproduced from Zilles K, Palomero-Gallagher N and Amunts K (2013) Development of cortical folding during evolution and ontogeny. *Trends in Neurosciences* 36, 275–284. doi: 10.1016/j.tins.2013.01.006.

function, presenting evidence that their complex folding patterns contribute to the organization, specialization, and integration of neural circuits.

In recent decades, advances in neuroimaging technologies, from high-resolution magnetic resonance imaging (MRI) to sophisticated diffusion imaging models, have revealed that cortical folds are not random but exhibit systematic relationships with functional organization, structural networks, and cognition. These relationships extend beyond primary sensory and motor cortices, with important implications for both local and global network organization.

The relationship between cortical folds and function becomes particularly apparent when examining how different types of sulci emerge during brain development. Primary sulci, which emerge first in gestation, are large in surface area, deep, and often coincide with primary sensory areas, such as the calcarine sulcus and primary visual cortex (e.g., area V1). At the other end of the spectrum, tertiary sulci emerge last in gestation, are smaller and shallower than primary sulci, and tend to be located in association cortices, which have expanded the most throughout evolution. During brain development, multiple converging factors, including genetic, cellular, and mechanical (which we discuss in subsequent sections of this chapter), guide the orderly emergence of cortical folds.

In humans, this process begins in utero, with key sulci forming along a relatively predictable timeline (**Chi et al., 1977**; **Welker, 1990**). Around 10 weeks of gestation, the first major indentations, the interhemispheric and transverse cerebral fissures, begin to form. By 14–16 weeks, the Sylvian fissure (lateral sulcus) appears as one of the earliest major sulci. This is followed by the central sulcus and other primary folds in the second trimester. Specifically, primary folds typically develop before 30 weeks, secondary folds around 32 weeks, and tertiary folds around 38 weeks or later (**Chi et al., 1977**; **De Vareilles et al., 2023**). Studies in nonhuman primates, particularly macaques (**Fukunishi et al., 2006**; **Kochunov, 2010**; **Sawada et al., 2009**), suggest a similar sequence of sulcal formation, though over a shorter gestational period. Notably, macaques lack tertiary sulci as observed in great apes, but do exhibit small, shallow dimples. As tertiary sulci are still being discovered in humans (**Willbrand et al., 2022b, 2024**), their developmental timeline needs to be revisited using modern fetal imaging methods, as their timeline is largely rooted in an empirical paper conducted nearly a half a century ago (**Chi et al., 1977**).

The morphological features of tertiary sulci hold particular significance for cognition due to their location in expanded association cortices. These features reliably correlate with individual differences in higher order cognitive functions, such as reasoning and executive abilities, and reliably predict the location of specialized functional areas and networks (**Miller et al., 2021b**; **Weiner et al., 2014**). Observations like these, along with others explored in this chapter, illustrate how cortical folding, shaped by a confluence of evolutionary, developmental, and mechanical factors, plays a crucial role in structuring the brain's wiring and functional architecture. By linking folding patterns to the emergence of specialized systems, such as language networks in the frontal lobe (**Hopkins et al., 2022**; **Li et al.,**

**2023**; **Schenker et al., 2010**), researchers are uncovering how structural adaptations in primate brains support sophisticated cognitive functions. Furthermore, empirical findings showing that individual variations in folding patterns can predict behavioral outcomes opens new avenues in clinical research, offering the potential for more precise diagnoses and intervention strategies for neurodevelopmental and psychiatric conditions.

This chapter explores these themes with a balance of breadth and depth, providing targeted examples throughout each section. We begin by examining how cortical folding shapes brain function, influences local circuit operations, and affects large-scale network dynamics that support perception and cognition. We then address the "death of a dogma" detailing how recent evidence reveals a strikingly precise relationship among sulci (presence/absence; morphological features), function, and cognition, countering long-held assumptions. While we acknowledge exceptions in structural-functional-cognitive relationships that provide important insights into perceptual and cognitive brain systems, accumulating empirical evidence shows that these relationships are more the norm than the exception across cortex. They are not limited to primary sensory cortices, as classically thought, but extend to association cortices as well. This becomes particularly compelling when examining detailed folding features such as sulcal bumps (local outward protrusions of the cortical surface within sulci), pits the deepest points within individual sulci that often correspond to the points of initial folding during development, and evolutionarily novel tertiary sulci (**Arcaro et al., 2020**; **Miller et al., 2021b**; **Natu et al., 2021**). Building on this foundation, we delve into the evolution of specialized systems, such as object recognition and language networks, where distinct folding patterns are tightly linked to advanced perceptual and cognitive functions. To understand how these specializations emerge over development and broader evolutionary timescales, we examine the fundamental mechanisms of cortical folding, detailing how mechanical forces, cellular processes, and genetic innovations interact to shape the intricate architectures of primate brains. These mechanisms not only define the physical structure of the cortex but also provide the foundation for understanding how brain structure supports function. We will draw from the sequence and timing of sulcal formation (detailed above for primary, secondary, and tertiary sulci), and how this developmental trajectory establishes the framework for neural processing. By mapping typical sulcal development, we gain critical insight into how disruptions in these patterns contribute to developmental and neurological disorders. We consider clinical applications, illustrating how sulcal morphology informs diagnostics and interventions, and conclude by considering unanswered questions and the potential for emerging tools and methodologies to advance future discoveries regarding sulcal-functional relationships.

A central theme throughout this chapter is that cortical folding is far from arbitrary. Instead, it reflects a complex interplay between form and function that has guided the evolutionary trajectory of primate brains and continues to shape individual differences in cognition and disease susceptibility.

## 2 How cortical folding shapes brain function

The architectural and connectivity distinctions between gyri and sulci shape neural computation, from local circuit operations to large-scale network dynamics that support various perceptual and cognitive processes. Early histological studies (**Bok, 1929**; **von Economo and Koskinas, 1925**; among others) revealed that cortex on gyri is consistently thicker than cortex lying within sulci. Von Economo and Koskinas made particularly important contributions by improving measurement techniques, cutting histological slices perpendicular to the axes of gyri and sulci, which revealed gradual decrease in cortical thickness from gyral crowns to sulcal depths. Modern imaging and histology have confirmed these systematic differences in cortical thickness, neuronal density, and laminar composition across (**Fig. 2**A-C). Gyri typically exhibit thicker cortices with more sharply defined layers, vertically oriented myelinated fibers, and expanded deeper layers. Sulci tend to have thinner cortices, less sharply defined laminar boundaries, and often exhibit more horizontally oriented fibers, though this pattern can vary depending on cortical region (**Hilgetag and Barbas, 2005, 2006**; **Llinares-Benadero and Borrell, 2019**). These differences between sulci and gyri are broadly consistent with Bok's principle, which predicts that mechanical tension during folding leads to expansion of deeper layers in gyri while superficial layers may be relatively compressed, potentially leading to a thinner overall profile in sulci (**Bok, 1929**; **Welker, 1990**). In contrast to these structural distinctions, findings regarding neuronal density across cortical folds are mixed. **Hilgetag and Barbas (2006)** report that neuronal density in upper and deep cortical layers does not significantly differ between gyral, intermediate, or sulcal cortices when controlling for overall layer volume, suggesting that any apparent increase in cell packing in sulci is largely a consequence of reduced cortical thickness rather than a true increase in absolute cell number. In contrast, **Llinares-Benadero and Borrell (2019)** describe sulcal regions as having denser cell packing, potentially reflecting differences in column structure and the relative distribution of neurons across layers, without explicitly controlling for overall layer volume.

Beyond broad differences between gyri and sulci, cortical thickness varies along sensory processing hierarchies. Primary cortical areas tend to be thinner than higher-order regions, suggesting that these architectural variations support increasingly complex computations along cortical processing streams (**Hilgetag and Barbas, 2005**; **Wagstyl et al., 2015**). Genetic factors contribute to the variations as well (**Burt et al., 2018**; **Gomez et al., 2019**; **King and Weiner, 2024**). However, there are notable exceptions to these variations. For example, unlike human primary sensory regions, the human primary motor cortex is exceptionally thick. Together, these variations in cortical architecture underscore how folding establishes microenvironments tailored to specific computational demands, forming a foundation for functional specialization across cortex.

Beyond differences in structure, connectivity patterns also vary systematically across gyri and sulci. Histological analyses in non-human primates indicate that gyri often contain dense, long-range axonal pathways that facilitate interactions between distributed networks, supported by broad horizontal connections that promote integrative processing (**Hilgetag and Barbas, 2006**) (**Fig. 2**D). In contrast, sulci more commonly contain shorter, locally confined connections optimized for regional processing (**Hilgetag and Barbas, 2006**;

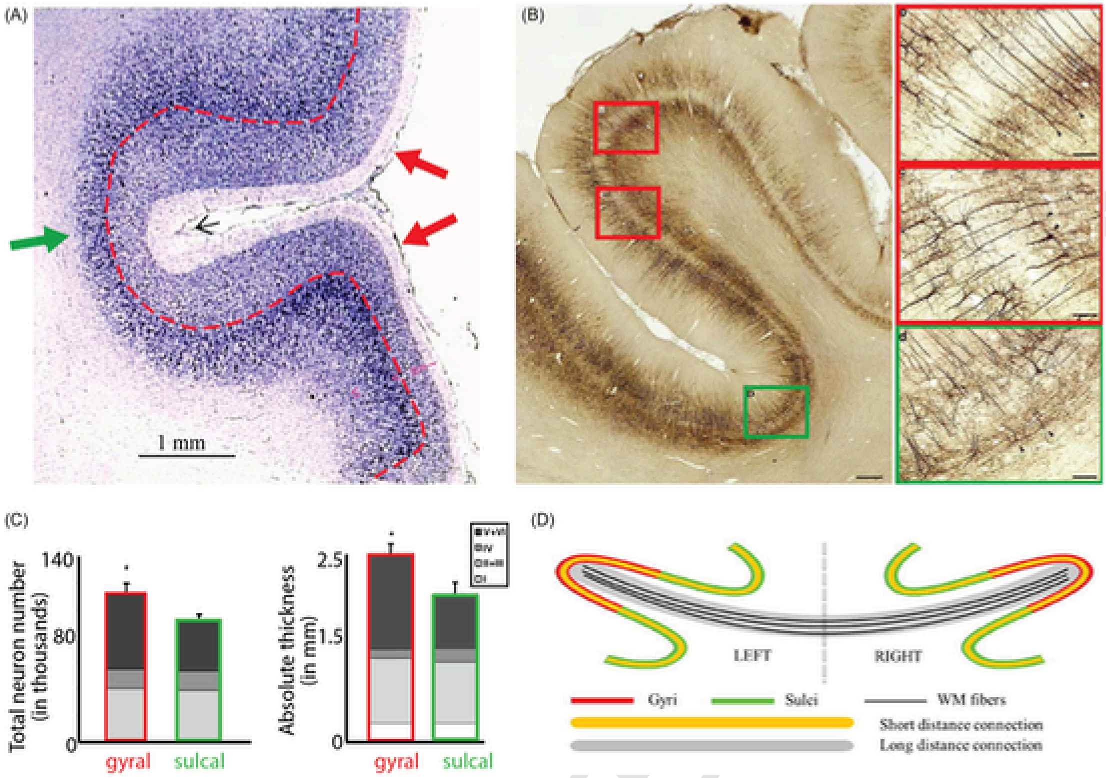

**Fig. 2** Structural and Functional Implications of Cortical Folding. (A) Layer-specific variations in cortical thickness. Coronal section of rhesus monkey medial prefrontal cortex showing expanded deep layers in gyri (large arrows) and reduced thickness in sulcal depths (arrowhead). (B) Mechanical influences on cellular morphology. SMI-32 staining of pyramidal neurons in a coronal section of the macaque arcuate sulcus. Neurons in sulci are more densely packed with compact dendritic structures, while those in gyri are more spaced out. (C) Neuron density and cortical thickness. A quantitative comparison of neuronal distribution under 1 $mm^2$ of cortical surface showing more neurons and greater thickness in gyral cortical columns. (D) A functional model of gyri and sulci. Schematic depicting gyri as hubs for long-range connections (black fibers) and sulci as centers for local processing (yellow fibers), illustrating the role of cortical folding in network organization. Image reproduced from: (A) Hilgetag CC and Barbas H (2006) Role of mechanical factors in the morphology of the primate cerebral cortex. *PLoS Computational Biology* 2: e22. doi: 10.1371/journal.pcbi.0020022; (B and C) Hilgetag CC and Barbas H (2005) Developmental mechanics of the primate cerebral cortex. *Anatomy and Embryology (Berlin)* 210: 411–417. doi: 10.1007/s00429-005-0041-5; (D) Deng F, Jiang X, Zhu D, Zhang T, Li K, Guo L, Liu T (2013) A functional model of cortical gyri and sulci. *Brain Structure & Function* 219: 1473–1491. doi: 10.1007/s00429-013-0581-z.

**Zilles et al., 2013**). Diffusion MRI studies in both human and non-human primates provide further support for this differentiation, indicating that gyri generally have denser and longer projections than sulci (**Deng et al., 2013**). However, it is important to note that diffusion MRI may underestimate long-range connections in sulci due to the dense, locally confined superficial fibers in these regions, which can obscure deeper projections (**Reveley et al., 2015**). Additionally, sulci tend to exhibit more tangentially oriented projections, while gyri favor a radial organization (**Smart and McSherry, 1986**; **Welker, 1990**). Strikingly, at the macroscale, cortical folding also governs the ratio of white to gray matter. The final folded configuration of the cortex, rather than sheer neuron count or simple wiring constraints, determines how extensively white matter expands across diverse mammalian species (**Mota et al., 2019**). In other words, cortical surface area and thickness, along with the mechanical and energetic constraints that drive folding, determine the relative expansion of white and gray matter. Together, these observations illustrate how cortical folds shape both local microcircuitry and large-scale connectivity patterns that support complex brain functions.

Recent advances in high resolution imaging and improved methods for resolving fine scale cortical features have further clarified links between folding patterns and functional networks. For instance, sulcal pits appear to maintain consistent relationships with higher-order networks across individuals (**Amiez et al., 2019**; **Im et al., 2010**; **Natu et al., 2021**), suggesting that local, anatomical features of the cortex provide predictable anchors for particular functional areas and networks. Sulcal pits, which are the deepest points of sulci, are postulated to be the first regions to form during development, and have been theorized to play a role in functionally specialized cortical networks (**Im et al., 2010**; **Markowitsch and Tulving, 1994**; **Rakic, 1988**). Comparative studies indicate that relationships between sulcal morphology and function persist across primates with widely varying brain sizes and degrees of gyrification (**Mars et al., 2018**). That is, folds themselves help guide neural communication, with sulcal pits supporting more localized short-range circuits while gyral crowns facilitate more distributed long-range connections across cortical networks (**Nie et al., 2012**; **Van Essen et al., 2014**). More recent work also highlights a more complex picture, with some core sulcal regions, including sulcal pits, serving as highly interconnected "communication hubs," potentially forming the backbone of long-range network communication (**Kruggel and Solodkin, 2023**).

Collectively, these findings underscore that cortical folds are not merely topographical quirks, but rather organizational frameworks, closely linked to both local and large-scale connectivity. Even subtle differences in folding geometry can be associated with variation in functional organization across individuals, potentially reflecting differences in computational processes (**Im et al., 2010**; **Lopez-Persem et al., 2019**; **Amiez et al., 2013**). Through their relationship with fiber pathways and network topology, cortical folds are a critical feature in how neural signals propagate and integrate across the brain's diverse functional regions.

## 3 Death of a dogma: Precise structural-functional coupling

While modern methods increasingly reveal that cortical folds reflect fundamental aspects of cortical organization, historically, many researchers viewed sulci as unreliable markers of brain structure, favoring cytoarchitectonic and myeloarchitectonic features instead. Nevertheless, **Cunningham (1892)** and **Smith (1907)** argued that while sulci do not always mark precise transitions between areas, sulci consistently align with distinct cortical areas and fall into two main types: axial and limiting. Axial sulci identify cortical areas, such as the primary visual cortical area (V1) within the calcarine sulcus, whereas limiting sulci mark transitions between functionally distinct areas, such as the mid-fusiform sulcus, which separates four cytoarchitectonic areas on the lateral and medial sides of the human fusiform gyrus (**Weiner, 2019**). **Smith (1907)** emphasized this general point, writing:

> "In my earlier communication I have insisted on the fact that in the process of folding of such a plastic material as cerebral cortex we find that as a rule sulci do not develop with mathematical precision at the exact boundary lines of adjoining areas or in the precise axis of any given territory. But while fully realizing the accuracy of Professor Sherring-ton's observation that they are not reliable as landmarks, we cannot be blind to the fact that each one of the vast majorities of the furrows on the surface of the hemisphere presents a definite causal relationship to some given cortical area (or areas)." **Smith, 1907**, pp. 237–238.

As an historical aside, Cunningham was once dubbed as a "Dublin anatomist" by *Nature* editors in **Benham (1897)** in an article summarizing Parker's work on the role of soap bubbles and tension to cortical folding (**Parker, 1896**; **Weiner, 2014**). This early theory is consistent with more recent tension-based accounts of cortical folding (**Van Essen, 1997**) and its subsequent refinements (**Van Essen, 2020**). Recent advancements in neuroimaging and precision imaging approaches have decisively overturned the historical dogma that sulci are unreliable indicators of brain organization, revealing remarkably precise relationships between cortical folding and functional organization. These relationships extend beyond early emerging and evolutionarily conserved primary sulci, which are well established in primary sensory and motor areas, to later-developing secondary and tertiary sulci that exhibit greater variability across species and individuals. These findings also illustrate the need to recognize when structure-function relationships hold, while also identifying cases where they do not. The next sections examine these correspondences from primary sensory regions to higher-order association cortices, along with evolutionary adaptations that have led to increasingly specialized functions.

## 4 Structure-function relationships within primary sulci

One of the strongest challenges to the classical view that cortical folds are functionally irrelevant comes from primary sensory and motor areas in humans. While primary folds have long been recognized as landmarks for sensory and motor maps (**Fig. 1**), specific folding features within these sulci have been shown to reliably correspond to distinct functional representations. The central sulcus, for example, serves as a critical boundary between the primary motor cortex (precentral gyrus) and primary somatosensory cortex (postcentral gyrus). Within this sulcus, high-resolution functional imaging and intracortical recordings have identified an omega-shaped fold, known as the "hand knob", which reliably marks the portion of motor cortex controlling hand movements, making it an essential landmark for both research and clinical practice (**Guan et al., 2023**; **Yousry et al., 1997**) (**Fig. 3**A). Neurosurgeons routinely rely on the hand knob to avoid resecting areas essential for fine motor control during surgeries for conditions such as epilepsy or tumors (**Caulo et al., 2007**). Furthermore, individual differences in the morphology and size of the central sulcus have been linked to variations in local white matter architecture (**Pron et al., 2021**), species differences (**Hopkins et al., 2022**) and to motor expertise. For example, pianists and athletes show localized adaptations in the cortical hand representation, reflecting experience-dependent plasticity in motor areas (**Amunts et al., 1997**).

The human visual system provides another striking example of precise structure-function coupling. The calcarine sulcus reliably anchors the retinotopic organization of the primary visual cortex (V1), with different positions along the sulcus corresponding to distinct regions of the visual field. Specifically, the upper bank of the calcarine sulcus maps to the lower visual field, while the lower bank corresponds to the upper visual field (**Wandell and Winawer, 2011** for modern and historical perspectives). Within this sulcus, several small internal gyri, referred to as "rungs", align with specific eccentricities in the visual field (**Schira et al., 2012**) (**Fig. 2**B). This topographic precision enables researchers to predict functional organization from anatomical features alone (**Benson et al., 2012, 2014**). However, variability exists within this regularity and is meaningful for visual perception. For example, the surface area of V1 can vary more than threefold across individuals (**Benson et al., 2022**) and differences in the surface area of the calcarine sulcus correspond to individual differences in visual perception of object size (**Schwarzkopf et al., 2011**). Moreover, the depth and curvature of the calcarine

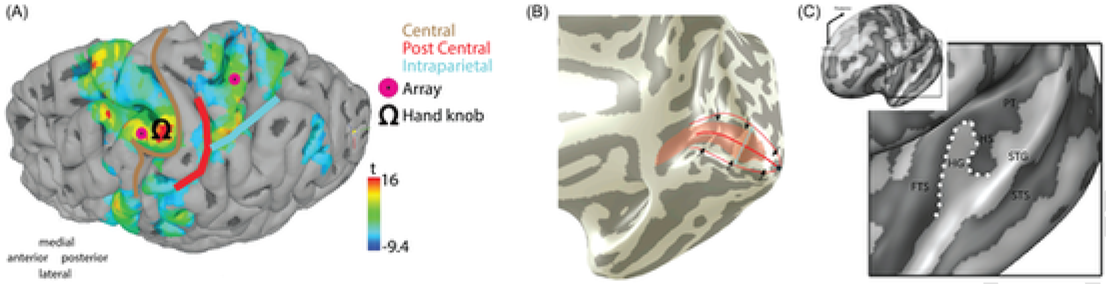

**Fig. 3** The Relationship between Functional Maps and Sulcal Morphology. (A) The "hand knob," a distinct omega-shaped fold in the central sulcus, corresponds to neural representations of hand movements in the primary motor cortex. (B) Inflated cortical surface of human occipital cortex shows internal gyri ("rungs", indicated by arrows) within the calcarine sulcus (transparent red) corresponding to specific eccentricities in the visual field. Light gray represents gyri and dark gray represents sulci. (C) Heschl's gyrus (white dotted line), the anatomical locus of the primary auditory cortex (A1), exhibits a systematic tonotopic organization, with sulcal morphological variations linked to differences in auditory processing. Image reproduced from: (A) Guan C, Aflalo T, Kadlec K, Gámez De Leon J, Rosario ER, Bari A, Pouratian N and Andersen RA (2023) Decoding and geometry of ten finger movements in human posterior parietal cortex and motor cortex. *Journal of Neural Engineering* 20: 036020. doi: 10.1088/1741-2552/acd3b1; (B) Schira MM, Tyler CW, Rosa MGP (2012) Brain mapping: The (Un)Folding of striate cortex. *Current Biology* 22: R1051–R1053. doi: 10.1016/j.cub.2012.11.003; (C) Moerel M, De Martino F, Formisano E (2014) An anatomical and functional topography of human auditory cortical areas. *Frontiers in Neuroscience* 8. doi: 10.3389/fnins.2014.00225.

sulcus have been correlated with variations in cortical magnification and thereby visual acuity (**Dahlem and Tusch, 2012**), underscoring how cortical folding shapes perceptual capacity.

In the human auditory domain, the relationship between cortical folding and function is similarly robust. Heschl's gyrus, which houses the primary auditory cortex (A1), exhibits distinct tonotopic organization, with different sound frequencies mapped systematically along its surface. Research has shown that small variations in the length, curvature, and number of Heschl's gyri correlate with auditory processing abilities, such as pitch discrimination and speech perception (**Da Costa et al., 2011**) (**Fig. 3**C). In some individuals, the presence of additional sulci within Heschl's gyrus has been associated with enhanced musical aptitude, further highlighting the functional consequences of anatomical variability (**Moerel et al., 2014**). Importantly, these structural features are not static; they can adapt over time. For example, longitudinal studies suggest that auditory training can induce changes in the cortical organization of Heschl's gyrus, emphasizing the dynamic interplay between anatomy and function (**Herholz and Zatorre, 2012**). This plasticity over an individual's lifespan reflects broader variability observed across evolutionary timescales. Heschl's gyrus itself is an evolutionarily recent structure absent in macaque monkeys, illustrating how cortical folding patterns have changed across primates to support specialized auditory functions. We expand on these evolutionary considerations later in this chapter.

Taken together, these observations highlight how primary sulci, such as the central and calcarine sulci, and gyri like Heschl's, provide a topographical and functional framework for basic sensorimotor and sensory processes. Rather than being arbitrary wrinkles, these landmarks (considered *axial* by **Cunningham, 1892**) reliably delineate neural representations across individuals, offering vital insights for clinical applications (e.g., neurosurgical planning) while also revealing fundamental principles about how brain structure and function co-evolve.

## 4.1 Sulcal-function relationships beyond primary cortex

Precise structure-function relationships extend far beyond the primary sensorimotor regions and into association cortices. While an exhaustive list is beyond the scope of this chapter, we highlight striking recent findings that demonstrate the role of sulci in functionally specialized systems across different cortical areas, including those supporting higher perceptual and cognitive functions.

In the human ventral temporal cortex, the mid-fusiform sulcus serves as a reliable anatomical predictor of the fusiform face area(s) (FFA), while the deepest point of the collateral sulcus consistently aligns with the parahippocampal place area (PPA) (**Natu et al., 2021**; **Weiner et al., 2014**; Chen et al., 2023) (**Fig. 4**A). These regions, critical for face and scene recognition, respectively, exhibit functional selectivity that often mirrors the depth and morphology of the underlying sulcus. Subtle variations in folding, such as the development of tertiary sulci, appear to refine and compartmentalize these computations, linking anatomical landmarks to perceptual expertise and complex visual recognition **Weiner and Zilles (2016)**. Similarly, in the human dorsal visual stream, sulcal landmarks are tied to visuospatial processing and motor planning. Segments of the intraparietal sulcus (IPS) are consistent anatomical landmarks for attentional and spatial areas involved in eye-hand coordination, object manipulation, and goal-directed movements (**Schluppeck et al., 2005**; **Silver and Kastner, 2009**). Even lateralized functions, such as tool selectivity, exhibit a systematic coupling with cortical folding (**Chao and Martin, 2000**; **Mruczek et al., 2013**).

Shifting focus to the human frontal cortex, a region distinguished by numerous tertiary and evolutionarily novel sulci, many of which are unique to humans and absent in other primates including great apes (**Amiez et al., 2019**; **Willbrand et al., 2023a**; **Amiez et al.,**

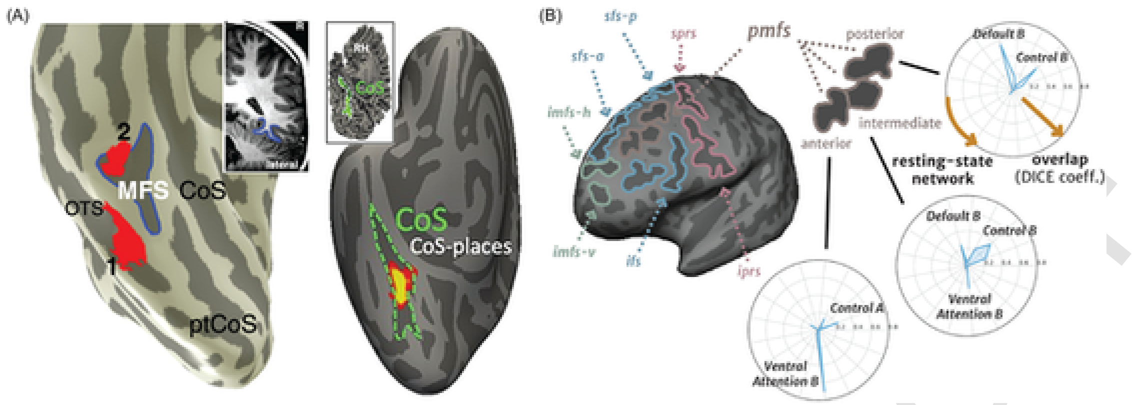

**Fig. 4** Sulcal Anchors for High-Level Perceptual and Cognitive Processing. (A) Category-selective regions in ventral temporal cortex align with sulcal landmarks. Left: Inflated right cortical surface of a human brain, with face-selective regions (red) mapped relative to the mid-fusiform sulcus. Right: Probabilistic maps show the most probable location of place-selective CoS-places (also known as the PPA) within the collateral sulcus (CoS). Warmer colors indicate greater overlap of place-selective responses across participants. Abbreviations: OTS, occipital temporal sulcus; MFS, mid-fusiform sulcus; CoS, collateral sulcus (B) Tertiary sulci in the lateral prefrontal cortex (LPFC) serve as stable sulcal anchors. Left: Inflated left hemisphere from an individual brain, with distinct tertiary sulci in LPFC outlined in different colors, where each color corresponds to a specific sulcus. Right: Polar plots showing the resting-state functional connectivity of three posterior middle frontal sulci (pmfs) across 17 large-scale networks, illustrating distinct connectivity profiles. Image reproduced from: (A) Weiner KS, Golarai G, Caspers J, Chuapoco MR, Mohlberg H, Zilles K, Amunts K and Grill-Spector K (2014) The mid-fusiform sulcus: A landmark identifying both cytoarchitectonic and functional divisions of human ventral temporal cortex. *NeuroImage* 84: 453–465. doi: 10.1016/j.neuroimage.2013.08.068; Natu VS, Arcaro MJ, Barnett MA, Gomez J, Livingstone M, Grill-Spector K, Weiner KS (2021) Sulcal depth in the medial ventral temporal cortex predicts the location of a place-selective region in macaques, children, and adults. *Cerebral Cortex* 31: 48–61. doi: 10.1093/cercor/bhaa203; (B) Miller JA, D'Esposito M, Weiner KS (2021a) Using tertiary sulci to map the "Cognitive Globe" of prefrontal cortex. *Journal of Cognitive Neuroscience* 33: 1698–1715. doi: 10.1162/jocn_a_01696.; Miller JA, D'Esposito M and Weiner KS (2021a) Using tertiary sulci to map the "Cognitive Globe" of prefrontal cortex. *Journal of Cognitive Neuroscience* 33: 1698–1715. doi: 10.1162/jocn_a_01696.

**2023a, 2023b**), reveals equally compelling examples of structure-function relationships that highlight its specialized roles in cognition, motor planning, and control. For example, the frontal eye fields align predictably with the precentral sulcus, underscoring their role in voluntary eye movements and attentional control (**Amiez and Petrides, 2009**). Similarly, the supplementary eye fields (SEF), positioned within the superior frontal gyrus, show a relationship to sulcal geometry, particularly in regions implicated in planning and error monitoring during saccadic eye movements (**Grosbras, 1999**). More broadly, tertiary sulci across the lateral prefrontal cortex (LPFC) serve as stable structural markers corresponding to distinct large-scale functional networks. The characteristic connectivity patterns of individual frontal sulci reinforce their role in organizing executive and cognitive control processes (**Willbrand et al., 2023a**; **Miller et al., 2021a**; **Fig. 4**B). Their presence and morphology reliably predict functional subdivisions within LPFC, illustrating that even small, evolutionarily recent folds contribute to shaping neural computations and specialization.

Beyond just sulci themselves or sulcal depth, sulcal intersections are also functionally meaningful. For example, the intersection of the posterior portion of the superior frontal sulcus and the superior precentral sulcus reliably identifies an eccentricity cluster (**Mackey et al., 2017**). Similarly, the supplementary motor area (SMA) aligns with the cingulate sulcus, extending from a rostral pre-SMA segment (between the genu of the corpus callosum and a vertical plane through the anterior commissure) to a more caudal SMA-proper segment (**Vorobiev et al., 1998**). This organization collectively supports higher-order motor planning, including selection and sequencing of movements, as well as execution processes (**Ikeda, 1999**). Even language processing, one of the most uniquely human cognitive abilities, showcases a remarkable relationship of cortical folding to function, with the inferior frontal sulcus serving as a reliable landmark for syntactic and semantic integration regions (**Fedorenko et al., 2012**). For a more exhaustive list focused on the prefrontal cortex, see (**Weiner et al., 2024**; **Weiner et al., 2025**). Thus, from perceptual expertise in object and face recognition to attention, visuomotor control, motor planning, and executive control, sulcal morphology provides stable structural landmarks that scaffold functional specialization and network organization, far more systematically than previously assumed.

## 4.2 Individual differences and functional implications

Variability in cortical folding across individuals provides a powerful lens for understanding how structural differences shape cognitive abilities, developmental trajectories, and vulnerability to neurological conditions. For example, the depth and morphology of sulci in prefrontal cortex have been shown to predict performance on executive tasks such as reasoning and working memory (**Voorhies et al., 2021**; **Yao et al., 2023**). Similarly, the paracingulate sulcus, a region with notable inter-individual variability (present in 70–75% of left and 50–60% of right hemispheres in neurotypical populations), correlates with cognitive control and reality monitoring, and its presence or absence has been linked to differences in specific cognitive ability and introspective processes (**Buda et al., 2011**; **Fornito, 2004**). Beyond the frontal lobe, distinct sulcal patterns in the intraparietal sulcus have been associated with higher performance in language tasks involving comprehension and production (**Santacroce et al., 2024**), as well as numerical cognition (**Roell et al., 2021**).

Additionally, atypical sulcal patterns are often early indicators of neurodevelopmental conditions. For example, shallow or absent sulci in specific cortical regions have been associated with autism severity (**Brun et al., 2016**) and schizophrenia risk (**Chakirova et al., 2010**; **Lavoie et al., 2014**; Yücel et al., 2002). Moreover, disruptions to sulcal development can foreshadow challenges in cognitive and motor functions. For instance, sulcal anomalies in the inferior frontal gyrus have been linked to language deficits (**Clark and Plante, 1998**), while sulcal abnormalities in the orbitofrontal cortex are associated with impairments in emotion regulation and social cognition (**Watanabe et al., 2014**; **Whittle et al., 2014**) as well as anosmia (**Hummel et al., 2003**).

Finally, developmental studies further illustrate how sulcal patterns align with the maturation of cognitive functions. The morphology of specific sulci in the ventral temporal cortex, such as the occipito-temporal sulcus, is associated with reading abilities (**Borst et al., 2016**; **Cachia et al., 2018**). A stable sulcal pattern emerging during gestation in the left intraparietal sulcus, specifically whether it is "sectioned" by a perpendicular branch, predicts arithmetic abilities in children and adolescents (**Schwizer Ashkenazi et al., 2024**). Additionally, prefrontal sulcal development tracks improvements in executive function during adolescence, shedding light on the structural underpinnings of prolonged cognitive maturation in humans (**Willbrand et al., 2022a, 2022b**; **Willbrand et al., 2024**; **Willbrand et al., 2023c**). Specifically, the combination of these empirical findings likely reflect that the extended developmental window of secondary and tertiary sulci coincides with critical periods of cellular maturation and circuit refinement, allowing these later-forming regions to adapt to environmental influences and cognitive demands. As such, these later folds may provide additional cortical "real estate" for cognitive flexibility, complex learning, and species-specific capabilities such as language. These developmental patterns further reinforce that cortical folding plays a crucial role in shaping individual differences in cognition and behavior.

### 4.3 Arguing against the dogma: Broader significance

These findings collectively challenge the outdated notion that cortical folds are merely incidental or unreliable landmarks. Instead, they reveal a precise and dynamic coupling between structure and function that spans the entire neocortex, from primary sensory and motor maps to higher-order cognitive domains. This coupling in association cortices was particularly surprising and only became evident when examining the more variable tertiary sulci and specific morphological features within them, such as pits (**Im et al., 2010**; **Natu et al., 2021**) and bumps (**Arcaro et al., 2020**). This shift in perspective profoundly reshapes our understanding of brain organization and individual variability in cognition, establishing sulcal patterns as robust markers for core functional regions and predictors of key developmental and clinical outcomes. While exceptions exist, the overall correspondence between sulcal anatomy and function emerges as a fundamental principle of brain organization.

Understanding when and where these correspondences occur is not only essential for elucidating sulcal-functional relationships in cognition but also has direct practical applications. Neurosurgeons routinely rely on sulcal landmarks, such as the central sulcus "hand knob", to minimize resection-induced motor deficits (**Caulo et al., 2007**; **Yousry et al., 1997**). More broadly, sulci function as "surgical corridors", helping to navigate the brain and reduce damage to surrounding tissue during procedures (**Tomaiuolo et al., 2022**; **Tomaiuolo and Giordano, 2016**). Looking ahead, leveraging these reliable structure-function relationships may advance diagnostic and therapeutic strategies, from identifying at-risk children for reading or socio-cognitive deficits to personalizing surgical planning based on each individual's unique folding patterns. We revisit this idea later in the chapter.

By demonstrating that sulcal variability tracks meaningful differences in cognition and development, modern neuroscience has firmly established cortical folding as a critical determinant of brain function. In short, the accumulating empirical evidence shows that sulci are not just simple, randomly appearing cortical "wrinkles". Instead, they are central to the anatomical microarchitecture and areal organization that shape the cortical network blueprint guiding perception, action, and thought.

## 5 Evolution of specialized systems

Having established that cortical folds and function are tightly coupled in the human brain more than historically appreciated, we now turn to how these relationships vary across primate species. The systematic links between folding and function offer a unique window into the emergence and evolution of specialized brain systems. By comparing species with varying brain sizes and ecological demands, we observe both conserved structure-function relationships and morphological refinements. These evolutionary changes often involve the development of new sulci and tertiary folds, enhancing core capabilities, from basic sensory processing to advanced cognitive functions such as language, executive control, and social cognition. Small morphological modifications layered upon a conserved cortical framework have catalyzed significant leaps in perception and cognition, ultimately distinguishing humans from other primates. This section builds on extensive foundational work (**Borrell, 2018**; **Kroenke and Bayly, 2018**; **Van Essen, 2007**; **Welker, 1990**; **Zilles et al., 2013**, among others).

## 5.1 Evolutionary patterns

Cortical folding has evolved in tandem with increasing brain size and cognitive complexity across primates. Allometric analyses confirm that as primates evolved larger brains, gyrification, the process of forming folds, rose in a largely predictable manner (**Finlay and Darlington, 1995**; **Hofman, 1985**). However, this relationship is not uniform across the cortex. Association cortices, particularly in the frontal and parietotemporal regions, exhibit disproportionate expansion relative to simple scaling (**Chaplin et al., 2013**; **Hill et al., 2010**). This differential expansion reflects region-specific increases in neuronal proliferation, leading to greater volumetric growth and subsequent mechanical forces that drive cortical folding (as detailed in **Section 5**) Thus, cortical folding is not merely a byproduct of increasing brain size, but rather an evolving architectural adaptation shaped by functional demands and evolutionary pressures. Remarkably, a similar pattern is observed within human populations, where individuals with larger brains exhibit disproportionately greater cortical surface area, mirroring the evolutionary pattern across primates (**Toro et al., 2008**). These observations suggests that the disproportionate expansion of regions supporting higher-order functions such as abstract reasoning and social cognition may arise in part through general principles of brain scaling.

Despite substantial differences in brain size and cortical morphology, many aspects of cortical folding reflect a conserved developmental blueprint across primates. Primary sulci, including the central sulcus and lateral (Sylvian) fissure, are present across all gyrencephalic primates, establishing a foundational anatomical framework early in ontogeny. Secondary and tertiary sulci emerge later, exhibiting graded evolutionary variation in prominence and segmentation. This conserved developmental progression from primary to tertiary sulci sequence suggests a structured evolutionary process that maintains a core cortical scaffold.

Nonetheless, evolutionary trajectories show distinct lineage-specific elaboration, particularly involving secondary and tertiary sulci. Comparative analyses across multiple primate species, including humans, chimpanzees, baboons, and macaques, demonstrate graded variation in sulcal prominence and continuity (**Amiez et al., 2023a, 2023b**; **Willbrand et al., 2024**; **Willbrand et al., 2022a**). In primates with relatively smaller brains, such as macaques and baboons, tertiary sulci often manifest as transient dimples or short segments rather than continuous folds, reflecting intermediate degrees of cortical elaboration. In larger brained primates, including humans and chimpanzees, these sulci become increasingly pronounced, continuous, and structurally differentiated, supporting finer subdivisions of cortical areas critical for complex cognition and social behavior (**Amiez et al., 2019, 2023a, 2023b**). For example, the principal sulcus in macaques, historically considered a single structure, comprises multiple segments topologically corresponding to distinct secondary and tertiary folds in human dorsolateral prefrontal cortex (**Amiez et al., 2023a, 2023b**). Similarly, simpler dimples observed in macaque and baboon brains correspond topologically to more elaborated sulci, such as the paracingulate and superior precentral sulci, in humans. However, caution is warranted in interpreting these evolutionary comparisons, as all modern species are equally evolved and none represent ancestral states. Indeed, fossil evidence indicates that cortical evolution followed distinct trajectories across primate lineages. For example, complex sulcal patterns emerged prior to major increases in brain size in Old World monkeys, whereas substantial brain expansion preceded sulcal elaboration in hominoids (**Gonzales et al., 2015**). These lineage-specific differences highlight that cortical folding follows conserved developmental patterns, but also reflects substantial evolutionary diversity presumably driven by distinct adaptive pressures.

Studies of cortical folding in closely related hominids provide important insights into human-specific evolutionary changes. Certain tertiary sulci show remarkable consistency between humans and other hominids. For example, the middle frontal sulcus (MFS) in humans is also present in chimpanzees, but absent in nonhominid primates, suggesting a functional role associated with the cortex in this sulcus that emerged later in primate evolution (**Miller et al., 2021**) (**Fig. 5**A). Probabilistic areal distinctions derived from human cortical anatomy can predict tertiary sulcal locations in chimpanzee association cortices, including ventral temporal and lateral prefrontal regions (**Hathaway et al., 2023**; **Miller et al., 2020**) (**Fig. 5**B). Other tertiary sulci, however, show distinct human specialization. The paracingulate sulcus in medial prefrontal cortex, absent in baboons and macaques, shows a distinctive leftward asymmetry in humans that is absent in chimpanzees (**Amiez et al., 2019**) (**Fig. 5**C). Similarly, the inframarginal sulcus (IFRMS) in medial parietal cortex and the paraintermediate frontal sulci in lateral PFC appear more frequently in humans than chimpanzees (**Hathaway et al., 2023**; **Willbrand et al., 2023b**) (**Fig. 5**D). Collectively, these findings illustrate how comparative analyses of closely related hominids reveal both shared and uniquely human cortical specializations.

## 5.2 Evolutionary adaptations in structure-function relationships

While foundational structure-function relationships are conserved across species, evolutionary pressures have refined these couplings to support species-specific adaptations. These shifts across primate evolution are apparent even at the earliest stages of cortical processing. For example, the calcarine sulcus, which anchors V1, exhibits species-specific retinotopic mappings. In humans, it predominantly represents central visual representations e.g., the cortical magnification factor (**Wandell and Winawer, 2025**), whereas in macaques, it emphasizes peripheral representations (**Arcaro et al., 2022**) (**Fig. 7**A). These variations are not solely due to an enlarged foveal representation. Instead, expansions and additional folding of lateral association cortices may have displaced V1 medially (**Polyak, 1957**), or this shift may have emerged from changes in the initial patterning of thalamocortical projections. Similarly, structural differences in the motor cortex reveal species-specific adaptations. For example, the morphology of the hand knob varies across hominids, reflecting differences in motor control demand (**Foubet et al., 2024**), further demonstrating how evolutionary pressures shape cortical organization to meet species-specific needs (**Krubitzer and Seelke, 2012**).

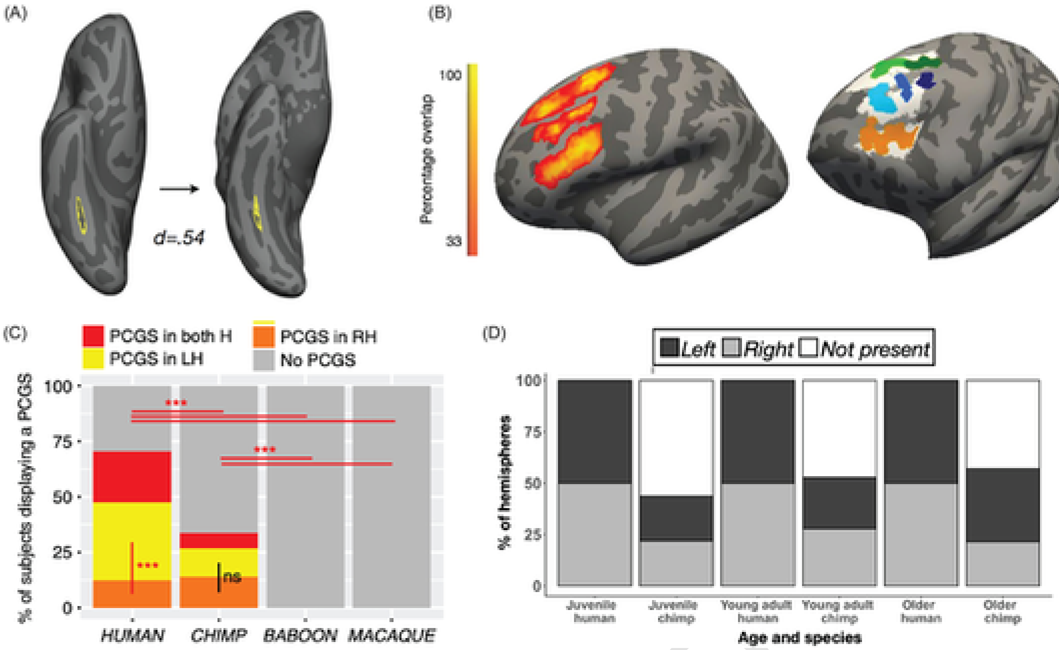

**Fig. 5** Cross-species comparison of cortical sulci: conserved and variable features. (A) Left: Inflated cortical surface showing the human mid-fusiform sulcus (MFS) in yellow. Right: Example chimpanzee right hemisphere, showing that the MFS is a consistent feature in hominoid brains (but absent in Old World monkeys, such as macaques (not shown)). (B) Left: Inflated human cortical surface with probabilistic sulcal definitions in the lateral prefrontal cortex. Right: Corresponding human probabilistic sulcal projections (white) mapped onto an individual chimpanzee hemisphere. The superior (green) and inferior (orange) frontal sulci are identifiable in chimpanzees, along with smaller tertiary sulci in the middle frontal gyrus (blue), guided by human predictions. (C) Incidence rates of the paracingulate sulcus (PCGS) across species. Baboons and macaques lack a PCGS, while humans, but not chimpanzees, show a leftward asymmetry. (D) Incidence rates of the inframarginal sulcus (IFRMS) across species and age groups. The IFRMS is more frequently absent in chimpanzees compared to humans. Adapted from: (A) Miller JA, Voorhies WI, Li X, Raghuram I, Palomero-Gallagher N, Zilles K, Sherwood CC, Hopkins WD and Weiner KS (2020) Sulcal morphology of ventral temporal cortex is shared between humans and other hominoids. *Scientific Reports* 10: 17132. doi: 10.1038/s41598-020-73213-x; (B) Hathaway CB, Voorhies WI, Sathishkumar N, Mittal C, Yao JK, Miller JA, Parker BJ and Weiner KS (2023) Defining putative tertiary sulci in lateral prefrontal cortex in chimpanzees using human predictions. *Brain Structure & Function* 229: 2059–2068. doi: 10.1007/s00429-023-02638-7; Amiez C, Sallet J, Hopkins WD, Meguerditchian A, Hadj-Bouziane F, Ben Hamed S, Wilson CRE, Procyk E, Petrides M (2019) Sulcal organization in the medial frontal cortex provides insights into primate brain evolution. *Nature Communications* 10: 3437. doi: 10.1038/s41467-019-11347-x; Willbrand EH, Parker BJ, Voorhies WI, Miller JA, Lyu I, Hallock T, Aponik-Gremillion L, Koslov SR, Alzheimer's Disease Neuroimaging Initiative, Bunge SA, Foster BL and Weiner KS (2022a) Uncovering a tripartite landmark in posterior cingulate cortex. *Science Advances* 8: eabn9516. doi: 10.1126/sciadv.abn9516.

Comparative imaging studies in macaques, chimpanzees, and humans further reveal how morphological differences enhance computational capacity. The superior temporal sulcus (STS) has expanded substantially in hominids compared to non-hominid primates. In humans, the posterior STS contains three branches, or *rami*, supporting multisensory integration crucial for semantic processing (**Petrides, 2023**). Similarly, novel tertiary sulci in the lateral parieto-occipital junction posterior to the STS branches have been linked to spatial orientation (**Willbrand et al., 2024**) and may serve as a transition between perception and memory (**Steel et al., 2021**).

Furthermore, sulcal refinements play a pivotal role in higher visual and perceptual functions. For instance, the mid-fusiform sulcus is a hominoid-specific structure closely linked to face perception (**Grill-Spector and Weiner, 2014**; **Weiner et al., 2014**; **Parvizi et al., 2012**). Building on that foundation, recent results show that face-selective regions in macaques also have a relationship with cortical morphology. In contrast to the sulcal-functional coupling in humans, the structural-functional coupling in macaques occurs with gyral bumps (**Arcaro et al., 2020**) (**Fig. 6**B) (Labels for colored sulci shown in the key are provided in Table S1 in the online version at https://doi.org/10.1016/B978-0-443-27380-3.00029-4). Even sulci present in other primates, such as the occipito-temporal sulcus (OTS), support uniquely human abilities like reading (**Weiner and Yeatman, 2020**). For example, longitudinal changes in a cortical gap within the OTS predict improvements in reading ability, an effect mediated by underlying white matter properties (**Bouhali et al., 2024**). Altogether, morphological refinements of sulci in human temporo-occipito-parietal cortices correlate with increasing perceptual and social complexities, highlighting their role in the evolution of novel functional capabilities.

Differential patterns of cortical expansion further explain why some structure-function relationships are better preserved than others. The medial VTC maintains a highly consistent relationship between sulcal depth and functional organization across species, likely due to

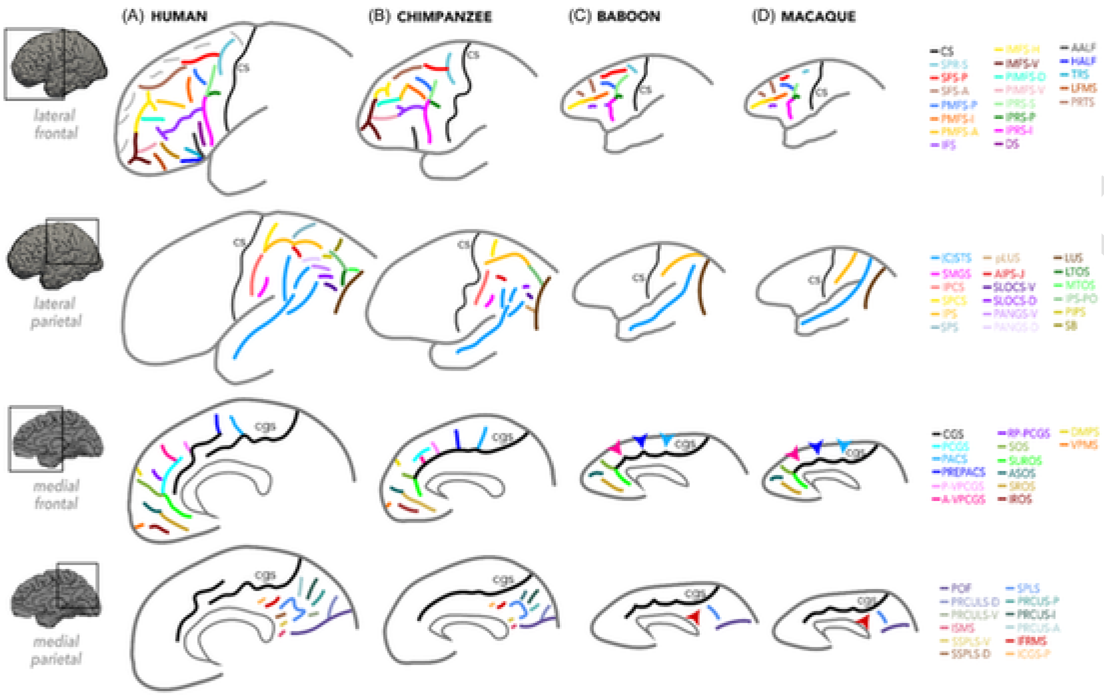

**Fig. 6** Evolutionary examples of cortical sulci across primates. Schematic comparison of sulci (colored lines) in lateral and medial frontal and parietal regions across primate species: (A) human, (B) chimpanzee, (C) baboon, and (D) macaque. Arrows indicate small dimples. Some sulci are hominoid-specific and have cognitive implications across development and clinical populations. Abbreviations: cs, central sulcus; cgs, cingulate sulcus.

its minimal cortical expansion compared to the rest of the brain. For example, despite the human brain being approximately 15 times larger than that of the macaque, face-selective regions remain adjacent to shallow sulci (posterior middle temporal sulcus in macaques; mid-fusiform sulcus in humans), while place-selective regions are located within deeper sulci (OTS in macaques; CoS in humans) (**Natu et al., 2021**) (**Fig. 7**B). This preservation persists despite major shifts in absolute anatomical positioning, reinforcing the stability of fundamental structure-function relationships throughout primate evolution.

Intriguingly, these evolutionary patterns align with postnatal development. Regions in the medial VTC show positive correlations between evolutionary and postnatal expansion patterns, while regions in the anterior-lateral VTC show little or negative correlation (**Hill et al., 2010**) (**Fig. 7**C). This relationship may explain why some functional regions, such as the place-selective PPA, emerge earlier in development and retain more stable structure-function relationships across primates, whereas others, such as the face-selective FFA(s), follow a more protracted development and exhibit greater cross-species variability in their anatomical positioning (**Deen et al., 2017**; **Golarai et al., 2007**; **Natu et al., 2021**).

## 5.3 The emergence of novel folds and functional correlates

Beyond vision, the evolution of cortical folding has facilitated increasingly sophisticated processing capabilities, particularly evident in three key domains that we focus on given the scope of this chapter.

### *5.3.1 Language circuits: A distinctive evolutionary leap*

Language stands out among human cognitive capacities due to its hierarchical, recursive structure and reliance on symbolic communication, qualities absent in other primates. Folding patterns in the lateral prefrontal cortex (LPFC) and associated pathways have diverged substantially in humans, supporting the evolution of complex syntax, vocal articulation, and semantic processing. The human LPFC exhibits distinct tertiary sulci and gyral patterns that are either absent or far less developed in other primates. Fossil endocasts suggest that morphological expansions in the LPFC may have been tied to the evolution of speech (**Balzeau et al., 2014**). While chimpanzees share basic frontal folds, humans possess additional or deeper tertiary sulci in LPFC that correspond to key linguistic functions (**Hopkins et al., 2022**; **Li et al., 2023**; **Schenker et al., 2010**; **Amiez et al., 2023b**). Nevertheless, ongoing research suggests that certain PFC sulci in non-human primates may have evolutionary correlates to tertiary sulci in humans (**Amiez et al., 2023a, 2023b**; **Miller et al., 2021a**).

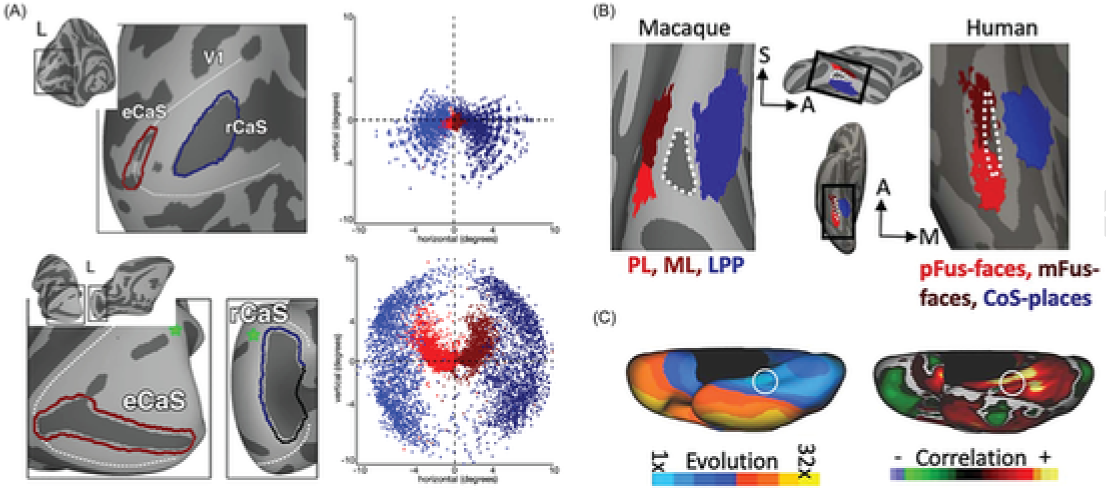

**Fig. 7** Cross-Species Sulcal Organization and Evolutionary Significance. (A) Calcarine sulci and visual field mapping in humans and macaques. Left: External (eCaS, red) and retrocalcarine (rCaS, blue) sulci in humans (top) and macaques (bottom), shown relative to V1 (white dotted outline). Right: Species differences in visual field coverage within eCaS (red) and rCaS (blue). (B) Sulcal boundaries for face- and place-selective regions. Left: In macaques, the posterior middle temporal sulcus (pmts, white) separates face- (ML, PL) and place-selective (LPP) patches. Right: In humans, the mid-fusiform sulcus (white dotted line) divides face- (mFus, pFus) and place-selective (CoS-places) regions. (C) Evolutionary and postnatal expansion of ventral temporal cortex (VTC). Left: Cortical expansion from macaques to humans, with minimal change in medial VTC (cool colors) and greater growth in anterior-lateral regions (warm colors); CoS-places marked (white circle). Right: Correlation between evolutionary and postnatal expansion, showing strong positive correlations medially and weak or negative correlations anterior-laterally. Image reproduced from: (A) Arcaro MJ, Livingstone MS, Kay KN and Weiner KS (2022) The retrocalcarine sulcus maps different retinotopic representations in macaques and humans. *Brain Structure & Function* 227: 1227–1245. doi: 10.1007/s00429-021-02427-0; (B) Natu VS, Arcaro MJ, Barnett MA, Gomez J, Livingstone M, Grill-Spector K, Weiner KS (2021) Sulcal depth in the medial ventral temporal cortex predicts the location of a place-selective region in macaques, children, and adults. *Cerebral Cortex* 31: 48–61. doi: 10.1093/cercor/bhaa203; (C) Natu VS, Arcaro MJ, Barnett MA, Gomez J, Livingstone M, Grill-Spector K and Weiner KS (2021) Sulcal depth in the medial ventral temporal cortex predicts the location of a place-selective region in macaques, children, and adults. *Cerebral Cortex* 31: 48–61. doi: 10.1093/cercor/bhaa203; Hill J, Inder T, Neil J, Dierker D, Harwell J and Van Essen D (2010) Similar patterns of cortical expansion during human development and evolution. *Proceedings of the National Academy of Sciences* 107: 13135–13140. doi: 10.1073/pnas.1001229107.

Language specialization also depends on long-range connectivity. The arcuate fasciculus, a major white matter tract connecting frontal and temporal language areas, has undergone structural modifications that align with cortical folding (**Catani and Thiebautdeschotten, 2008**; **Rilling et al., 2008**). As frontal sulci remodel to accommodate increasingly complex phonological and syntactic functions, the arcuate fasciculus and other language-related pathways appear to extend and reorganize along sulcal boundaries, forming the neural infrastructure for speech, grammar, and symbolic communication, an organizational complexity not observed in other primate vocal systems.

### *5.3.2 Executive function networks*

Executive networks in humans underlie skills, such as multi-step planning, rule-based problem-solving, and meta-cognition, that are rudimentary or absent in smaller-brained primates. The PFC has undergone substantial expansion through primate evolution (**Smaers et al., 2017**), marked by increasingly complex folding patterns that support higher-order cognitive abilities such as planning, cognitive control, and decision-making (**Weiner et al., 2024** for an extensive review across species). While many PFC sulci, including the superior frontal sulcus, are broadly conserved across Old World monkeys and hominids, recent work indicates that the frontopolar cortex is a notable exception, exhibiting substantial expansion in hominids but remaining relatively underdeveloped in other primates (**Amiez et al., 2023a, 2023b**). Further, although several sulcal landmarks are broadly preserved, certain regions in humans reveal elaborations absent in other primates. (**Petrides, 2012**). Tertiary sulci in the human PFC, which are either absent or underdeveloped in other primates, correlate strongly with executive abilities (**Miller et al., 2021a**; **Voorhies et al., 2021**; **Yao et al., 2023**, **Willbrand et al., 2023c**). These morphological refinements coincide with expansions in working memory and hierarchical reasoning circuits, facilitating the distinct functional zones that support monitoring, inhibiting, and flexible information manipulation. These capabilities, in turn, support sophisticated behaviors in tool use, social negotiation, and cultural innovation, areas where human abilities greatly exceed those of other primates.

### *5.3.3 Social cognition networks*

The evolution of social cognition is reflected in cortical folding patterns in regions dedicated to social perception, theory of mind, and empathic processing. The STS is integral for decoding biological motion, facial cues, and other social signals, and it shows systematic morphological differences across species. As noted earlier in this chapter, the human posterior STS contains a complex branching pattern not observed in other primates, supporting advanced social and semantic processing (though it is an open question if non-human hominoids also display a comparable branching pattern of the posterior STS). Additionally, humans exhibit an asymmetrical STS sulcal pit, a feature absent in non-human primates (**Leroy et al., 2015**). These morphological differences may provide a neuroanatomical scaffolding for supporting detailed analyses of motion and intention cues, which are essential for cooperation and complex group dynamics (**Basil et al., 2017**; **Deen et al., 2015**).

Beyond the STS, regions involved in theory of mind, such as the medial prefrontal cortex (mPFC) and temporoparietal junction (TPJ), exhibit distinct cortical folding and sulcal elaborations in humans. Comparative studies indicate that the human TPJ and surrounding branches of the STS may have evolved from cortical regions similar to those found in the macaque mid-STS. These macaque regions share similar functional connectivity profiles with human TPJ, but lack the expanded sulci and more complex neural network characteristics of humans (**Mars et al., 2013**). These structural differences may contribute to the capacity for increased processing of complex social information, including inferring the mental states of others. Similarly, the medial prefrontal cortex has undergone evolutionary changes in sulcal morphology and connectivity patterns that align with higher-order functions such as moral reasoning and abstract decision-making (**Neubert et al., 2014**). Together, these structural and functional adaptations reflect a shift from basic social awareness, which humans share with other primates, to the rich social cognition that underpins human language, culture, and empathy.

### 5.4 Filling gaps and integrating across domains: From morphological tweaks to cognitive leaps

Beyond these core domains, cortical folding influences a broad range of specialized networks. A unifying theme emerging from comparative studies is that conserved primate brain architectures provide a structural foundation for the emergence of new sulci and the expansion of existing ones, enabling complex and advanced functions. These “tweaks” in sulcal morphology confer the neuronal real estate and microstructural reorganization necessary for enhanced cognitive “leaps”.

Future comparative imaging and phylogenetic research is well positioned to refine our understanding of these processes, revealing how each newly deepened sulcal pit or emergent tertiary fold has contributed to the cognitive abilities that differentiate humans from other primates. This integrative approach will bridge the observed evolutionary changes in cortical folding to the genetic and developmental mechanisms underlying brain organization, setting the stage for a more comprehensive exploration of how folding patterns shape functional specialization, as discussed in the next section.

Later in the chapter, we will also explore how folding abnormalities serve as critical biomarkers for neurodevelopmental disorders and guide clinical interventions. Understanding the interplay of evolutionary, developmental, and functional factors that shape the folded cortex provides insight into the human brain’s evolutionary heritage, while highlighting its remarkable functional diversity.

## 6 Mechanisms of cortical folding

Building on previous sections in this chapter that illustrate how cortical folds correspond to function across primates, and that larger brains often show new sulci associated with advanced skills, we can now ask: What mechanisms contribute to the development and formation of such organized patterns? This inquiry naturally leads to a broader evolutionary question: Which of these mechanisms are conserved across primates, and how have these foundational processes been elaborated in humans, potentially contributing to their unique cognitive capacities?

To answer these questions, we emphasize that the intricate folding patterns of the human brain emerge from multiple levels of biological organization, spanning physical constraints of tissue growth, cellular dynamics of neurogenesis, and genetic innovations. As summarized in **Fig. 8**, several hypotheses attempt to explain these processes, including mechanical buckling due to differential cortical expansion, axonal tension-based models, and regionally localized cellular growth patterns. These perspectives highlight distinct yet complementary mechanisms contributing to the formation of sulci and gyri. For a more comprehensive discussion on the genetic, cellular, and biomechanical forces shaping cortical folding, we refer readers to recent reviews (**Borrell, 2018**; **Kroenke and Bayly, 2018**; **Llinares-Benadero and Borrell, 2019** are a few examples). Below, we highlight foundational and recent findings that illuminate the fundamental processes driving cortical folding.

### 6.1 Physical and mechanical principles

A fundamental insight into cortical folding arises from mechanical models demonstrating that when the cortex expands more rapidly than the underlying white matter, the tissue buckles to accommodate this growth (**Tallinen et al., 2014, 2016**). This buckling (or wrinkling) adheres to principles of elasticity: regions with greater expansion or higher stiffness form gyri, while more constrained areas become sulci (**Bayly et al., 2013**; **Garcia et al., 2018**) (**Fig. 8**). Notably, these principles are not exclusive to the brain. Similar mechanical forces shape the wrinkling of skin, the folding of intestinal villi, and other biological tissues where surface layers grow faster than their supporting structures (**Nelson, 2016**). These parallels highlight the universality of mechanical forces in shaping complex biological forms.

Mechanical forces act at multiple scales in the brain. Macroscopically, cortical growth differentials generate broad patterns of tension and compression. Microscopically, variations in cellular properties and tissue elasticity fine-tune local folding patterns (**Nelson, 2016**). Together, these global and local forces help explain the variability and consistency observed in folding patterns across species and individ-

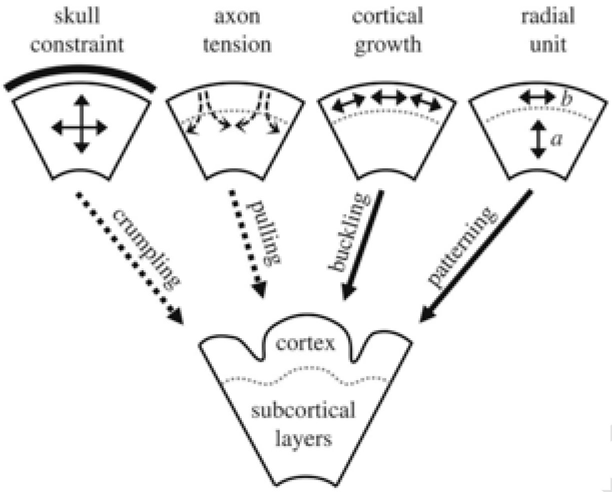

**Fig. 8** Theories of Cortical Folding Mechanisms. A summary of competing (or complementary) hypotheses explaining cortical folding. Some models emphasize differential cortical expansion and mechanical buckling, while others highlight axonal tension and connectivity-driven organization. Dotted arrows indicate mechanisms inconsistent with prior experimental findings, underscoring the need for further research to determine the dominant processes, or their combined contributions, to gyrogenesis. Image reproduced from Garcia KE, Kroenke CD and Bayly PV (2018) Mechanics of cortical folding: Stress, growth and stability. *Philosophical Transactions of the Royal Society B* 373: 20170321. doi: 10.1098/rstb.2017.0321.

uals (**Toro and Burnod, 2005**). From an evolutionary perspective, these mechanical principles help explain adaptations in cortical folding, particularly in larger primates, where increased gyrification preserves neural efficiency despite overall brain expansion. This folding allows maintenance of core functional networks while supporting the emergence of new, specialized functions, particularly within the highly expanded association cortices characteristic of humans.

### 6.1.1 *Interplay of mechanical forces and connectivity*

Mechanical constraints converge with axonal connectivity to shape folding. The tension-based theory of morphogenesis (**Van Essen, 1997**) proposes that axonal tracts exert pulling forces on the cortical sheet, effectively drawing interconnected regions closer together. This model helps explain why primary sensory areas tend to exhibit highly consistent folding patterns across individuals and species. The evolutionary conservation of these folds highlights their role in anchoring fundamental sensorimotor functions (**Rosa, 2002**). In contrast, association cortices, where newly formed and expanded tertiary sulci emerge (**Miller et al., 2021b**), reflect evolutionary flexibility. These expanded folding patterns may have been instrumental in supporting the emergence of complex cognitive behaviors, particularly those that distinguish human cognition from that of other primates.

However, axonal tension alone does not fully explain observed folding patterns. Computational and experimental studies reveal that differential cortical growth, regional tissue heterogeneity, and stiffness gradients also contribute to sulcal geometry (**Fig. 8**). For example, tangential cortical expansion drives localized buckling, particularly in rapidly growing association areas (**Xu et al., 2010**). Finite element simulations incorporating stiffness gradients and axonal forces reveal region-specific folding signatures (**Budday et al., 2014**; **Knutsen et al., 2013**). These findings align with an updated model of tension-based morphogenesis, which integrates interactions between tangential tension in outer cortical layers, growth-driven buckling, and local tissue heterogeneity (**Van Essen, 2020**). Such multifaceted models better capture the nuanced variations in cortical thickness, cellular composition, and elastic properties that lead to region-specific folding patterns. For example, association cortices undergo more pronounced expansion, and consequently more intricate folding than primary sensorimotor cortices. By integrating mechanical principles with connectivity-driven forces, researchers reveal how cortical folds emerge not from isolated mechanisms, but from synergistic processes. These folds contribute to efficient neural wiring, shaping patterns of functional communication across brain regions.

## 6.2 Cellular and molecular mechanisms

Beyond mechanical forces, cellular and molecular mechanisms orchestrate cortical folding by regulating neurogenesis and progenitor cell behavior. These cellular processes establish the structural and functional architecture of the brain, guiding the formation of gyri and sulci. Below, we discuss the role of progenitor cells, genetic innovations, and regional heterogeneities in shaping the brain’s morphology.

### *6.2.1 Progenitor cells and cortical expansion*

Radial glial cells, particularly outer radial glial cells (oRGs), play a pivotal role in gyrification (**Fietz et al., 2010**; **Hansen et al., 2013**; **Kriegstein et al., 2006**; **Lui et al., 2011**; **Rakic, 1995**). These specialized progenitors, enriched in gyrencephalic species, proliferate in the outer subventricular zone (oSVZ) and generate neurons essential for cortical expansion (**Borrell and Götz, 2014**; **Hansen et al., 2013**). The abundance and behavior of oRGs correlate with increased tangential cortical expansion and gyral complexity. In species such as ferrets, variations in intermediate radial glial cells, related to oRGs, mediate region-specific folding patterns (**Llinares-Benadero and Borrell, 2019**; **Reillo et al., 2011**) (**Fig. 8**).

In addition to oRGs, heterogeneous neurogenesis and migratory dynamics shape the distinct cellular compositions of gyri and sulci. Regions that form gyri undergo distinct proliferative and migratory events compared to those forming sulci (**Del Toro et al., 2017**; **Rockel et al., 1980**). For instance, radial glial divergence contribute to localized cortical thickening, particularly in gyral regions, while differences in adhesion molecules and migratory dynamics influences sulcal formation (**Llinares-Benadero and Borrell, 2019**; **Reillo et al., 2011**). Additionally, genetic regulation modulates these developmental events, as regional variations in gene expression drive differential cortical expansion and folding (**Mallela et al., 2020**; **Vasung et al., 2021**). Genetic analyses further reveal that cortical gyrification and overall brain size are influences by distinct sets of genetic factors, indicating independent regulatory pathways underlying these two aspects of cortical morphology (**Atkinson and Braddick, 2013**). Together, these region-specific progenitor dynamics, migratory patterns, and genetic factors establish the cellular and molecular basis for the complex folding of the cerebral cortex.

Human oRGs display distinct proliferative behaviors not observed in other primates, including prolonged cell cycles and unique patterns of cell division (**Nowakowski et al., 2017**; **Pollen et al., 2015**). Even small genetic or regulatory changes in these progenitor populations can produce large-scale morphological effects over evolutionary timescales, particularly regarding cortical thickness and folding. The evolutionary expansion of oRG populations, particularly in humans, underscores their role in enabling the dramatic increase in cortical surface area that supports advanced perceptual and cognitive functions.

### *6.2.2 Genetic drivers and local "hotspots"*

Genetic innovations have introduced molecular mechanisms that enhance progenitor cell proliferation and influence gyrification. Human-specific genes such as ARHGAP11B (**Florio et al., 2015**) and NOTCH2NL (**Fiddes et al., 2018**; **Suzuki et al., 2018**) expand progenitor pools and prolong neurogenesis in specific cortical regions, promoting sulcal and gyral elaboration. These genes are most active in association cortices (**Fiddes et al., 2018**; **Florio et al., 2015**), suggesting a potential link to advanced cognitive functions such as executive control, language, and abstract reasoning. Localized genetic activity creates hotspots of prolonged neurogenesis, particularly in regions with more intricate folding patterns that support specialized processing and higher-order functions. These hotspots, regulated by signaling pathways such as the Notch pathway, reinforce the link between genetic regulation, cortical folding, and functional specializations (**Llinares-Benadero and Borrell, 2019**).

## 6.3 Toward a "Fingerprint" of folds

In summary, cortical folding emerges from the dynamic interplay of mechanical forces, differential growth rates, and genetic influences, producing a distinctive "fingerprint" of folds in each species and individual. This fingerprint encapsulates both evolutionary history and adaptive innovations that underpin complex behaviors. Advances in imaging and histological techniques continue to refine our understanding of these factors, revealing how even subtle disruptions in progenitor behavior or gene regulation can result in cortical malformations and neurodevelopmental disorders, which we address next.

# 7 Neurosurgical, clinical, and translational implications

The recognition of sulcal patterns as critical anatomical markers in neurosurgery and clinical practice is often traced back to the Vogt-Vogt school, whose contributions influenced foundational work in cytoarchitecture and functional localization. The Vogts trained Brodmann and Sanides, among others (for reviews, see **Bailey et al., 1950**; **Bailey and von Bonin, 1951**; **Nieuwenhuys and Broere, 2017, 2023**; **Zilles and Amunts, 2010**).

Building on that legacy, both classic studies (**Penfield and Boldrey, 1937**) and modern neurosurgical approaches (**Tomaiuolo et al., 2022**) have demonstrated that sulci reliably predict the location of essential functions, shaping surgical strategies (**Parvizi and Kastner, 2018**). As our understanding of sulcal markers continues to advance, particularly tertiary sulci, they hold promise for furthering individualized medicine. Given their variability, sulci could serve as a "personalized coordinate system" for brain mapping (**Miller et al., 2021a**). More broadly, sulci function as "surgical corridors," providing access routes for neurosurgical interventions that minimize damage to brain areas critical for cognition, behavior, and movement (**Duchowny et al., 1996**; **Parvizi and Kastner, 2018**; **Ribas et al., 2006**; **Yousry et al., 1997**). For example, the anterior sylvian fissure is often opened to access the insula and deeper branches of the middle cerebral artery (**Ribas et al., 2006**).

Beyond surgical utility, sulcal patterns provide a window into structural-cognitive relationships across different clinical populations and developmental stages. For example, mapping electrode locations relative to sulcal patterning in individuals allows researchers to draw novel causal insights into functional and hemispheric specialization (**Mégevand et al., 2014**; **Parvizi et al., 2012**; **Rangarajan et**

**al., 2014**; **Rossion et al., 2018**). In neurodegenerative disorders, such as frontotemporal dementia or Alzheimer's disease, sulcal morphology offers potential diagnostic and prognostic value. Specific sulcal patterns may serve as early disease markers (**Harper et al., 2023**), and changes in sulcal morphology often precede clinical symptoms, making them promising markers of disease progression (**Hamelin et al., 2015**). Tertiary sulci, in particular, appear susceptible to age-related atrophy, with their structural changes predicting cognitive decline and impairments in executive function (**Maboudian et al., 2024**).

In younger populations, sulcal morphology has been linked to neurodevelopmental conditions. Certain occipitotemporal folding patterns predict future reading difficulties in individuals with dyslexia (**Cachia et al., 2018**), while atypical prefrontal sulcal configurations track with symptom severity and treatment response in individuals with ADHD (**Li et al., 2023**). Even subtle sulcal variations evident at birth or in early childhood can forecast later cognitive outcomes (**Cachia et al., 2008**; **Dubois et al., 2008**). Fetal and neonatal neuroimaging have revealed that deviations in sulcal depth, shape, or developmental timing by 30 weeks of gestation in preterm populations can foreshadow future language or motor difficulties (**De Vareilles et al., 2022**; **Dubois et al., 2008**; **Kersbergen et al., 2016**). Early detection of these variations enables targeted interventions, such as speech therapy, occupational therapy, or specialized educational support, for a number of neurodevelopmental disorders, potentially mitigating more severe functional impairments later in life (**Li et al., 2023**).

Sulcal morphology is also increasingly recognized as a potential biomarker for psychiatric conditions. For example, schizophrenia is associated with alterations in prefrontal sulci, especially within the paracingulate region, which correlate with disease onset and symptom severity (**Cachia et al., 2008**; **Garrison et al., 2015**). Further, sulcal patterns in the orbitofrontal cortex have been linked to cognitive and social deficits across multiple disorders (**Ongur and Price, 2000**), including schizophrenia (**Nakamura et al., 2007, 2020**; **Patti and Troiani, 2018**), autism spectrum disorder (**Watanabe et al., 2014**), attention deficit/hyperactivity disorder, and bipolar disorder (**Patti and Troiani, 2018**). These findings suggest that sulcal morphology could serve as a structural marker for psychiatric conditions and a transdiagnostic biomarker for shared neurodevelopmental pathways (**Hastings Iii et al., 2024**; **Willbrand et al., 2024**). Clinicians may be able to leverage sulcal patterning to improve precision of neuromodulation techniques such as transcranial magnetic stimulation (TMS). Calibrating coil placement according to sulcal geometry enhances the accuracy and efficacy of TMS-based interventions (**Fox et al., 2012**).

The presence or absence of evolutionarily variable tertiary sulci has particularly substantial implications for both cognition and clinical outcomes. The paracingulate sulcus is a compelling example: its presence and length are predictive of hallucination susceptibility in schizophrenia (**Garrison et al., 2015**) and correlate with impulsivity in a variety of psychiatric conditions (**Willbrand et al., 2024b**) (**Fig. 9**A). Similarly, the presence of a specific tertiary sulcus in the lateral prefrontal cortex, ventral para-intermediate frontal sulcus (pimfs-v), is associated with improvements in reasoning ability (**Willbrand et al., 2024a**; **Willbrand et al., 2022b**) (**Fig. 9**B). These findings reinforce the idea that evolutionarily novel tertiary sulci may contribute to uniquely human cognitive capabilities, while also serving as markers of individual differences in cognition and clinical vulnerability.

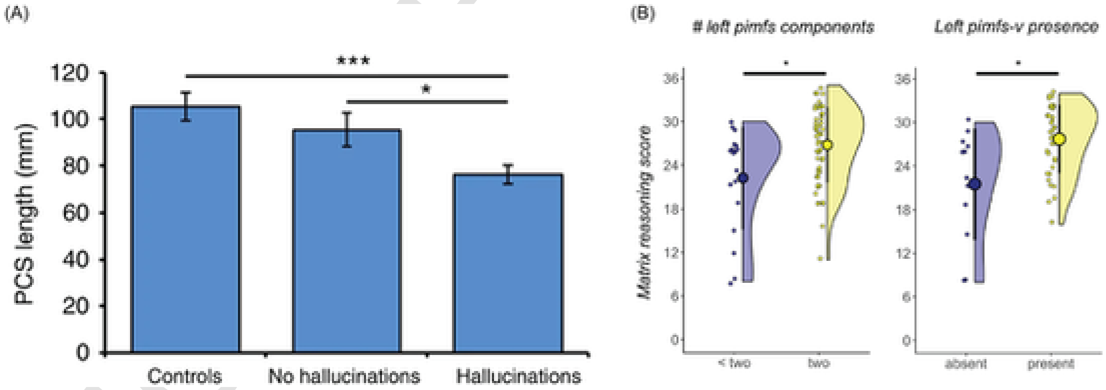

**Fig. 9** Clinical and cognitive significance of putative tertiary sulci. (A) Paracingulate sulcus (PCS) length across groups: neurotypical controls, individuals with schizophrenia without auditory hallucinations, and individuals with schizophrenia with auditory hallucinations. Shorter PCS length is associated with a higher likelihood of experiencing auditory hallucinations. (B) Reasoning performance as a function of the para-intermediate frontal sulcus (pimfs) components. Left: Individuals with two pimfs components show significantly better reasoning scores than those with only one component, controlling for age. Right: The presence of the ventral pimfs (pimfs-v) in the left hemisphere is associated with a significant reasoning advantage, observed both in age-matched subsamples and across the full dataset. Raincloud plots display individual data points, mean ± standard deviation, and kernel density estimates. Adapted from: (A) Garrison JR, Fernyhough C, McCarthy-Jones S, Haggard M (2015) The Australian Schizophrenia Research, Bank Carr V, Schall U, Scott R, Jablensky A, Mowry B, Michie P, Catts S, Henskens F, Pantelis C, Loughland C, Simons JS (2015) Paracingulate sulcus morphology is associated with hallucinations in the human brain. *Nature Communications* 6: 8956. doi: 10.1038/ncomms9956. (B) Willbrand EH, Parker BJ, Voorhies WI, Miller JA, Lyu I, Hallock T, Aponik-Gremillion L and Koslov SR Alzheimer's Disease Neuroimaging Initiative, Bunge SA, Foster BL and Weiner KS (2022a) Uncovering a tripartite landmark in posterior cingulate cortex. *Science Advances* 8: eabn9516. doi: 10.1126/sciadv.abn9516.

Altogether, cortical folding, once dismissed as a superficial anatomical feature, has become a promising tool for the diagnosis, prognosis, and treatment of neurological and psychiatric conditions. The historical notion that sulcal patterns represented an unstructured "chaos of the convolutions of the brain…were a better representation of a dish of macaroni than of the brain" (**Edinger, 1890**) has been decisively overturned. As machine learning techniques advance, our ability to detect, quantify, and interpret sulcal patterns at an individual level continues to improve (**Lee et al., 2024**; **Lyu et al., 2021**). Personalized sulcal maps may transform clinical protocols, combining precise anatomical mapping and advanced computational methods to develop novel prognostic tools, refine disease models, and enable earlier, more effective interventions, tailored to each patient's unique cortical architecture.

## 8 Future directions

Research over the last decade has greatly expanded our understanding of how cortical folding shapes brain function and evolution, yet many questions remain unanswered. This section highlights key areas where future studies can deepen our grasp of the mechanisms, evolutionary origins, and clinical implications of cortical folding.

### 8.1 Developmental trajectories

Although we have a general framework for the sequence of cortical folding during development, significant gaps persist regarding how specific folds emerge, stabilize, and interact with functional organization. Advances in fetal and neonatal imaging have supported longitudinal studies of early folding (**Dubois et al., 2021**), yet several fundamental questions remain:

1. How do genetic and environmental factors interact to shape the final pattern of folds?
2. What is the relationship between the timing of fold emergence and the onset of associated cognitive functions?
3. Can early folding patterns predict later cognitive or behavioral outcomes?

Large-scale imaging initiatives, such as the Human Connectome Project (**Van Essen et al., 2013**), offer an opportunity to revisit classic developmental timelines (**Chi et al., 1977**) using modern neuroimaging and updates sulcal definitions, including recognition of additional tertiary sulci in association cortices. Integrating these approaches with genetic and epigenetic data may help pinpoint specific genes and molecular pathways that drive regional folding differences, clarifying how certain patterns support specialized functions and contribute to individual differences in cognition.

### 8.2 Variability across species and interrelatedness

As covered in this chapter, both classical and modern studies and theoretical work have examined cortical folding patterns across species, yet key questions remain:

1. How do folding patterns and functions co-vary across a broad range of primate species?
2. Which folds are evolutionarily conserved, and which are more variable or uniquely emergent in larger-brained lineages?
3. How do these modifications enable novel cognitive capabilities?

Cross-species imaging studies, powered by consistent scanning and analytic methods, can reveal how cortical folding evolves alongside changes in behavior and cognition (**Mars et al., 2018**). Recent findings suggest that tertiary sulci in prefrontal regions may serve as particularly strong indicators of species-specific cognitive adaptations (**Amiez et al., 2019**; **Miller et al., 2021**; **Miller et al., 2021a**; **Willbrand et al., 2022a**). Investigating the relationship between individual variability and species-wide adaptations could provide new insights into both the evolutionary trajectory of folding and the developmental mechanisms that shape it.

### 8.3 Clinical applications and biomarkers

Beyond fundamental research, the clinical implications of sulcal–functional relationships merit deeper exploration:

1. Can early folding patterns help identify children at risk for neurodevelopmental disorders?
2. How might variations in folding inform personalized therapeutic strategies, from surgical planning to targeted neuromodulation?
3. Do certain folding abnormalities accelerate or predict disease progression in conditions in aging such as Alzheimer's disease or frontotemporal dementia?

Longitudinal imaging studies linking sulcal morphology to clinical outcomes may prove essential for establishing predictive biomarkers. As machine learning methods continue to advance, large clinical datasets could reveal subtle correlations between sulcal variations and disease risk (**Sun et al., 2022**). Eventually, these insights may enable automated screening tools capable of detecting high-risk folding patterns early in life, paving the way for timely interventions and improving long-term outcomes.

### 8.4 Methodological advances

Several technical challenges remain in the study of cortical folding:

1. Automated sulcal segmentation and labeling, particularly of tertiary sulci, remain a work in progress, especially across diverse species.
2. Comparisons of folding patterns across species are often hindered by a lack of standardized protocols, impeding direct replication across labs.
3. Integrating cortical maps across scales, from single-cell architecture to large-scale connectivity, remains an ambitious goal.

Recent strides in high-resolution imaging, machine learning–based morphometry, and standardized sulcal identification methods hold promise for addressing these challenges. Open science initiatives, including the sharing of raw MRI data and processing pipelines, are crucial for improving reproducibility and facilitating cross-laboratory comparisons.

### 8.5 Integration across levels

A major challenge ahead is synthesizing insights from multiple levels of biological organization, to form a unified model of how folding supports complex cognition. Key questions include:

1. How do cellular mechanisms of folding (e.g., outer radial glia proliferation) translate into macro-scale sulcal patterns?
2. How do local folds shape large-scale connectivity and emergent functional networks?
3. How have these mechanisms been modified during primate evolution to enable novel cognitive capabilities?

Addressing these questions requires an integrative approach that combines in vivo imaging, histological techniques, genetic data, and computational modeling. By bridging the gap between microstructural changes and the large-scale cognitive networks, future research could uncover universal principles governing cortical folding.

## 9 Conclusion

Understanding how cortical folds arise and evolve has broad implications, from advancing fundamental neuroscience and our understanding of the human mind to transforming clinical practice and precision medicine. As technological capabilities grow, from early developmental imaging to cross-species comparative techniques, researchers can probe both the mechanistic origins of sulcal formation and the evolutionary pressures that have driven new folds. By bridging scales from molecules to behavior, future studies may unlock a deeper understanding of cortical organization, revealing how subtle morphological changes have contributed to the perceptual and cognitive repertoire of the primate brain.

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