



# Using Tertiary Sulci to Map the “Cognitive Globe” of Prefrontal Cortex

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## Abstract

■ Stuss considered the human PFC as a “cognitive globe” [Stuss, D. T., & Benson, D. F. Neuropsychological studies of the frontal lobes. *Psychological Bulletin*, 95, 3–28, 1984] on which functions of the frontal lobe could be mapped. Here, we discuss classic and recent findings regarding the evolution, development, function, and cognitive role of shallow indentations or tertiary sulci in PFC, with the goal of using tertiary sulci to map the “cognitive globe” of PFC. First, we discuss lateral PFC (LPFC) tertiary sulci in classical anatomy and modern neuroimaging, as well as their development, with a focus on those within the middle frontal gyrus. Second, we discuss tertiary sulci in comparative neuroanatomy, focusing on primates. Third, we summarize recent findings showing the utility of tertiary sulci for understanding structural–functional relationships with functional network insights in ventromedial PFC and LPFC. Fourth, we revisit and update unresolved theoretical perspectives considered by

C. Vogt and O. Vogt (Allgemeinere ergebnisse unserer hirnforschung. *Journal für Psychologie und Neurologie*, 25, 279–462, 1919) and F. Sanides (Structure and function of the human frontal lobe. *Neuropsychologia*, 2, 209–219, 1964) that tertiary sulci serve as landmarks for cortical gradients. Together, the consideration of these classic and recent findings indicate that tertiary sulci are situated in a unique position within the complexity of the “cognitive globe” of PFC: They are the smallest and shallowest of sulci in PFC, yet can offer insights that bridge spatial scales (microns to networks), modalities (functional connectivity to behavior), and species. As such, the map of tertiary sulci within each individual participant serves as a coordinate system specific to that individual on which functions may be further mapped. We conclude with new theoretical and methodological questions that, if answered in future research, will likely lead to mechanistic insight regarding the structure and function of human LPFC. ■

## INTRODUCTION

The anatomy of the frontal lobe and its connections suggests a possible cognitive globe on which our knowledge of frontal lobe functions may be mapped. (Stuss & Benson, 1984)

Understanding how anatomical structures of the brain support functional networks underlying human-specific aspects of cognition is a major goal in cognitive neuroscience. Of the many anatomical structures to study, PFC is particularly important given its central role in cognitive control and goal-directed behavior (Stuss & Knight, 2013; Stuss, 2011; Miller & Cohen, 2001; Stuss & Alexander, 2000; Goldman-Rakic, 1995). Throughout his career, Don Stuss used maps of lesion damage to begin parcellating PFC into the component pieces of a “cognitive globe” as he described in the above quote (Stuss & Knight, 2013; Stuss & Alexander, 2000; Stuss & Benson, 1984). The composition of Stuss’ “cognitive globe” argued against the notion of PFC as a general “central executive” (Stuss, 2011).<sup>1</sup> Instead, Stuss’ “cognitive globe” within the frontal lobe consisted of several, interacting regions:

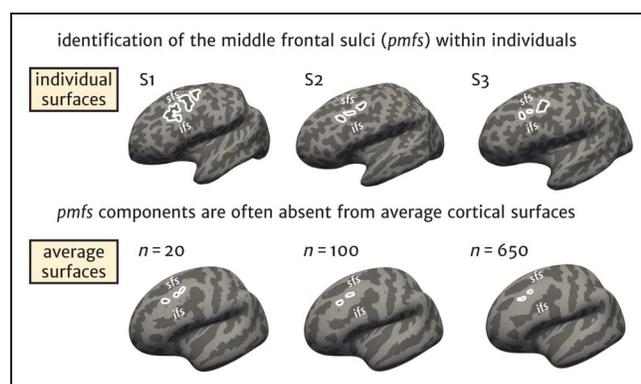
The frontal lobes (in anatomical terms) or the supervisory system (in cognitive terms) do not function (in physiological terms) as a simple

(inexplicable) homunculus.... Because of their extensive reciprocal connections with virtually all other brain regions, the frontal lobes may be unique in the quality of the processes that have evolved, and perhaps in the level of processing which might be labeled “executive” or supervisory. The different regions of the frontal lobes provide multiple interacting processes. (Stuss, Shallice, Alexander, & Picton, 1995, p. 206)

In the decades since Stuss’ original proposal, functional maps and parcellations of PFC at the scale of several centimeters have been developed across many cognitive domains using a variety of neuroimaging techniques. For example, modern neuroimaging research shows widespread support for a hierarchical functional gradient organized along the rostral–caudal axis of lateral PFC (LPFC; Demirtaş et al., 2019; Nee & D’Esposito, 2016; Reid et al., 2016; Badre & D’Esposito, 2009; Koechlin & Summerfield, 2007; Koechlin, Ody, & Kouneiher, 2003). Additionally, several different anatomical, functional, and multimodal approaches have further parcellated human LPFC into dozens of different areas (Kong et al., 2019; Eickhoff, Yeo, & Genon, 2018; Glasser et al., 2016; Sallet et al., 2013; Goulas, Uylings, & Stiers, 2012). Despite this progress, we still lack fundamental neuroanatomical details of the functional maps and parcellations within LPFC, largely for two main reasons. First, invasive methods

commonly used to uncover the neuroanatomical details of cortical networks in animal models cannot be used in humans. This is not a new issue and, over three decades ago, was summarized as the “backwardness of human neuroanatomy” (Crick & Jones, 1993). Second, human and nonhuman hominoid brains contain neuroanatomical structures that other primate brains lack. For instance, association cortices in hominoid brains contain shallow indentations known as tertiary sulci that are missing in the more lissencephalic brains of other species widely studied in cognitive neuroscience, such as mice, marmosets, and macaques (Petrides, 2019; Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Welker, 1990; Sanides, 1962).

Here, we propose that identifying and studying tertiary sulci contribute a “forwardness” to human neuroanatomy, as this approach offers an opportunity to examine neuroanatomical–functional relationships in humans that cannot be conducted in other animal models—even nonhuman hominoids. Specifically, we cannot map nonhuman hominoid brains in the way that we can map the human brain because of ethical reasons. As such, examining the relationship among tertiary sulci and different types of functional and neuroanatomical maps across spatial scales is a unique opportunity specific to the human brain. Consideration of tertiary sulci allows the “cognitive globe” of LPFC to be mapped within individuals without relying on an average cortical surface or template across individuals within which tertiary sulci commonly disappear (Figure 1). Consistent with Stuss’ approach to conduct neuropsychological and lesion mapping studies “within the frontal lobes with finer anatomical and experimental precision” (Stuss et al., 2005) than had been conducted previously, in this paper, we discuss recent research showing that tertiary sulci are useful for improving the scale of precision in anatomical–functional mapping in



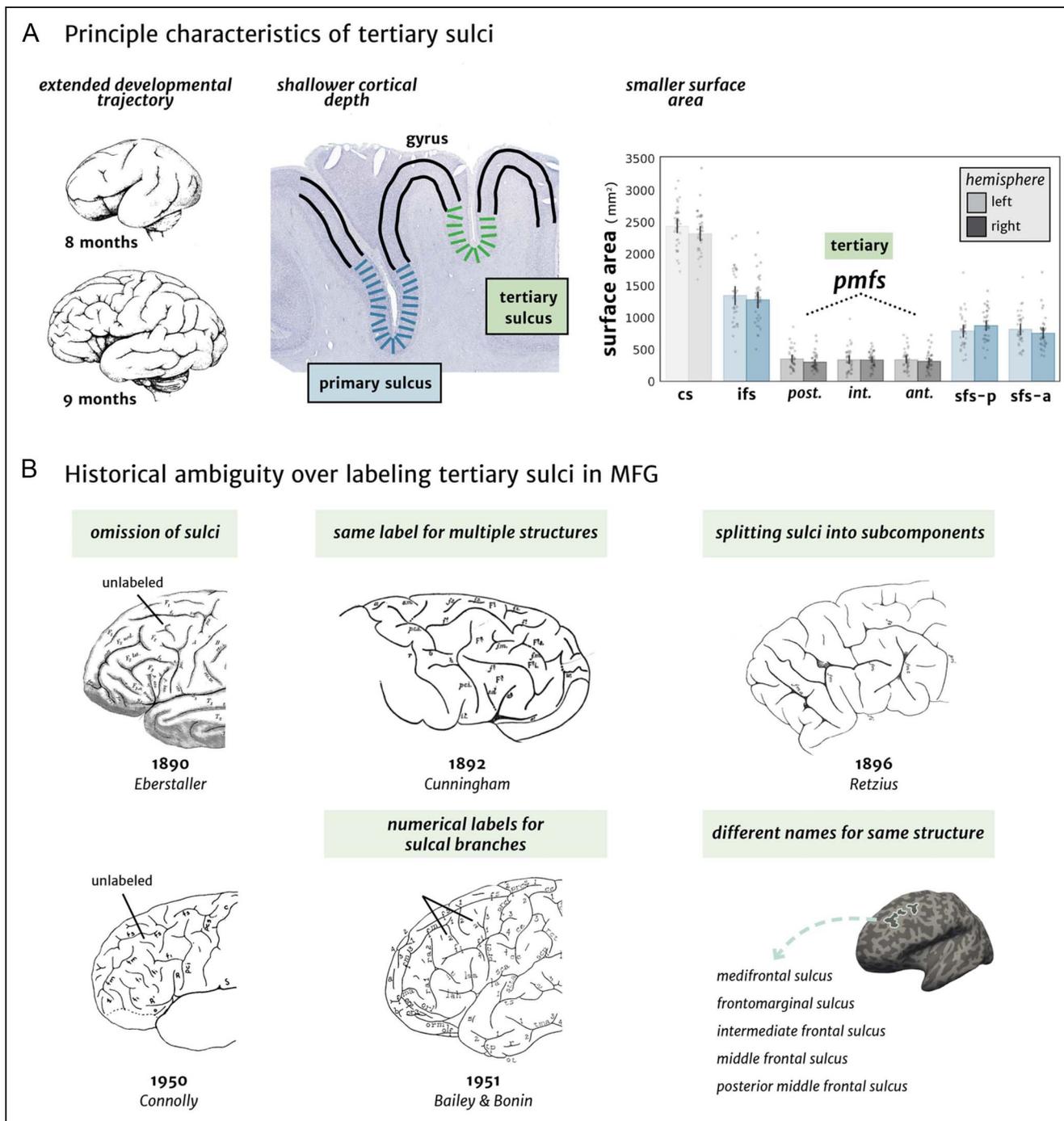
**Figure 1.** Tertiary sulci in LPFC disappear on averaged cortical surface reconstructions from anatomical MRIs. Top: three individually labeled left hemispheres with tertiary sulci in the MFG outlined in white. The superior and inferior frontal sulci (sfs, ifs) are labeled for reference above and below the MFG, respectively. Bottom: average cortical surfaces show much smaller tertiary sulci compared with individual participants. As more participants are included in the averaged cortical surface, tertiary sulci within the MFG disappear almost entirely, which is inconsistent with their prominence in individual hemispheres. Modified with permission from Miller, Voorhies, Lurie, D’Esposito, and Weiner (2021).

neuroimaging with translational and comparative applications with a particular emphasis on PFC. Specifically, we propose that tertiary sulci in the human cerebral cortex serve as a mesoscale coordinate map for linking neuroanatomical and functional properties of the human brain across spatial scales and modalities. The map of tertiary sulci within each individual participant serves as a coordinate system specific to that individual on which functions and additional anatomical features may be further mapped. That is, instead of a canonical atlas that typically uses an  $x, y, z$  coordinate system implemented in group analyses, in our suggested approach, tertiary sulci within each individual participant serve as a coordinate system specific to that individual in association cortices that often perform computations associated with human-specific aspects of cognition.

To link Stuss’ classic ideas with recent anatomical–functional findings, this review is divided into four main sections. First, we discuss LPFC tertiary sulci in classical anatomy and modern neuroimaging with a focus on those within the middle frontal gyrus (MFG). Second, we discuss tertiary sulci in development and comparative neuroanatomy, focusing on primates. Third, we summarize recent findings showing the utility of tertiary sulci for understanding structural–functional relationships in LPFC and likely in association cortices more broadly. Fourth, we revisit unresolved theoretical perspectives that tertiary sulci can serve as landmarks for cortical gradients. We conclude with new theoretical and methodological questions that, if answered in future research, will likely lead to mechanistic insight regarding the structure and function of LPFC.

## LPFC TERTIARY SULCI IN CLASSIC ANATOMY AND MODERN NEUROIMAGING: CLARITY VERSUS AMBIGUITY

It is widely accepted that LPFC is “phylogenetically novel” (Stuss & Benson, 1984) and is expanded in the human brain relative to nonhuman primate species commonly used in neuroscience research, such as rhesus macaques (Barrett et al., 2020; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012; Amiez & Petrides, 2009; Amiez, Kostopoulos, Champod, & Petrides, 2006; Croxson et al., 2005; Petrides, 2005; Petrides & Pandya, 1999). This “phylogenetically novel” LPFC includes additional anatomical structures such as tertiary sulci that are lacking in brains that are phylogenetically older. Tertiary sulci are so named for their developmental ordering, as they are the last sulci to emerge in gestation after the larger and deeper primary and secondary sulci (Figure 2A). It is also worth highlighting that there is a clear correlation among (i) the temporal emergence of a sulcus in gestation, (ii) the surface area of a sulcus, and (iii) the depth of a sulcus: Primary sulci emerge first and are largest/deepest, whereas tertiary sulci emerge last and are smallest/shallowest (Miller et al., 2020; Petrides, 2019; Weiner, 2019; Weiner & Zilles, 2016; Weiner et al., 2014; Welker, 1990; Chi, Dooling, & Gilles, 1977; Sanides, 1962, 1964; Bailey & von Bonin, 1951; Bailey, von Bonin,



**Figure 2.** Characteristics of tertiary sulci in LPFC and their historical identification. (A) Principle characteristics distinguishing tertiary sulci from larger primary sulci include later emergence in gestation and extended developmental trajectory (left), shallower sulcal depth (middle), and smaller surface area (right). Nissl stain (middle) downloaded from the Allen Human Brain Atlas ([human.brain-map.org/](http://human.brain-map.org/)), whereas developmental images (left) are adapted from Welker (1990). (B) We use the tertiary sulci in the posterior MFG as an example to outline the main types of ambiguity across postmortem studies leading to the neglect of some tertiary sulci in LPFC. Top and bottom left: Sulci in the MFG were depicted, but often left unlabeled (line) in official schematics as in Eberstaller (1890) and Connolly (1950). Top middle: Cunningham (1892) differentiated the “frontomarginal sulcus of Wernicke” (w) from the “sulcus frontalis medius of Eberstaller” (f.m.), in which the f.m. label included all tertiary sulci in the posterior MFG. Bottom middle: Tertiary sulci were identified and assigned letters, whereas sulcal branches were assigned numbers. Neither were given any distinguishing acronyms or labels in brain sections or schematics (Bailey & von Bonin, 1951). Top right: Separate labels were applied to different tertiary sulci within the posterior MFG. Retzius (1896) acknowledged a posterior transverse component (fmt) that was often distinct from the rest of the middle frontal sulcus. Ariëns Kappers (1928, 1929a) and Ariëns Kappers, Huber, and Crosby (1936) also acknowledged three components of the middle frontal sulcus (Appendix) largely consistent with the most modern and thorough schematic of sulcal morphology (Petrides, 2019), which identifies three components of the pmfs: an anterior, intermediate, and posterior (Petrides, 2019). Bottom right: Sulci within the MFG have been referred to using different labels, such as the medifrontal sulcus, frontomarginal sulcus, intermediate frontal sulcus, middle frontal sulcus, and pmfs, among others (see Appendix).

& McCulloch, 1950; Connolly, 1950; Turner, 1948; Retzius, 1896; Cunningham, 1892).

Ongoing research attempts to better understand the function of these evolutionarily new structures, some of which are likely unique to the human cerebral cortex. Specifically, large, freely available multimodal datasets have provided the ability to finally assess typical variations in tertiary sulcal morphology and functional organization within individuals that was not possible in classical studies of postmortem brains. Indeed, tertiary sulci were often excluded from classic neuroanatomical atlases because anatomists could not discriminate tertiary sulci from indentations produced by veins and arteries on the outer surface of the cerebrum in postmortem tissue, which is considered the gold standard of anatomical research (Weiner, Natu, & Grill-Spector, 2018). Consequently, the patterning of tertiary sulci within LPFC has a contentious history (Petrides, 2019; Petrides & Pandya, 2012), whereby tertiary sulci in LPFC were often undefined in classic atlases or contained different combinations of sulcal label mappings (Figure 2A; Appendix).

We highlight that modern neuroimaging methods contribute either clarity or ambiguity, depending on the methods used for definitions of tertiary sulci. In terms of clarity, defining tertiary sulci in cortical surface reconstructions of MRI data within individual participants produces an accurate representation of tertiary sulci because cortical surface reconstructions from MRI scans are made from the inner surface at the boundary between gray and white matter. As such, the definitions of tertiary sulci are clear and are not confusable with indentations produced by veins and arteries as in postmortem tissue. In terms of ambiguity, many researchers today analyze MRI data on cortical surfaces averaged across individuals (e.g., fsaverage, MNI152, and other cortical surface templates) that often do not accurately depict the patterning or location of tertiary sulci (Coalson, Van Essen, & Glasser, 2018; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). For example, our recent work shows that, even though a tertiary sulcus is present within every individual studied (Miller et al., 2021), it may shrink or disappear when cortical surfaces are averaged together because LPFC tertiary sulci are more variable in location and much smaller compared with primary and secondary sulci (Figure 1). For instance, the posterior middle frontal sulcus (pmfs), a tertiary sulcus in LPFC discussed throughout this review, is about five times smaller (in terms of surface area) and about half as deep as the primary central sulcus. Nevertheless, in other cortical expanses, such as ventral temporal cortex, tertiary sulci are preserved on average cortical surfaces (Miller et al., 2020; Weiner, 2019; Weiner et al., 2018). Thus, future studies will shed light on what anatomical and functional factors contribute to the variability and consistency of tertiary sulci in a given cortical expanse. Taken together, tertiary sulci have an unclear history for methodological reasons, which can be corrected with methods that instead preserve

neuroanatomical structures and take individual anatomical organization into consideration.

## **DEVELOPMENTAL TRAJECTORY OF LPFC TERTIARY SULCI**

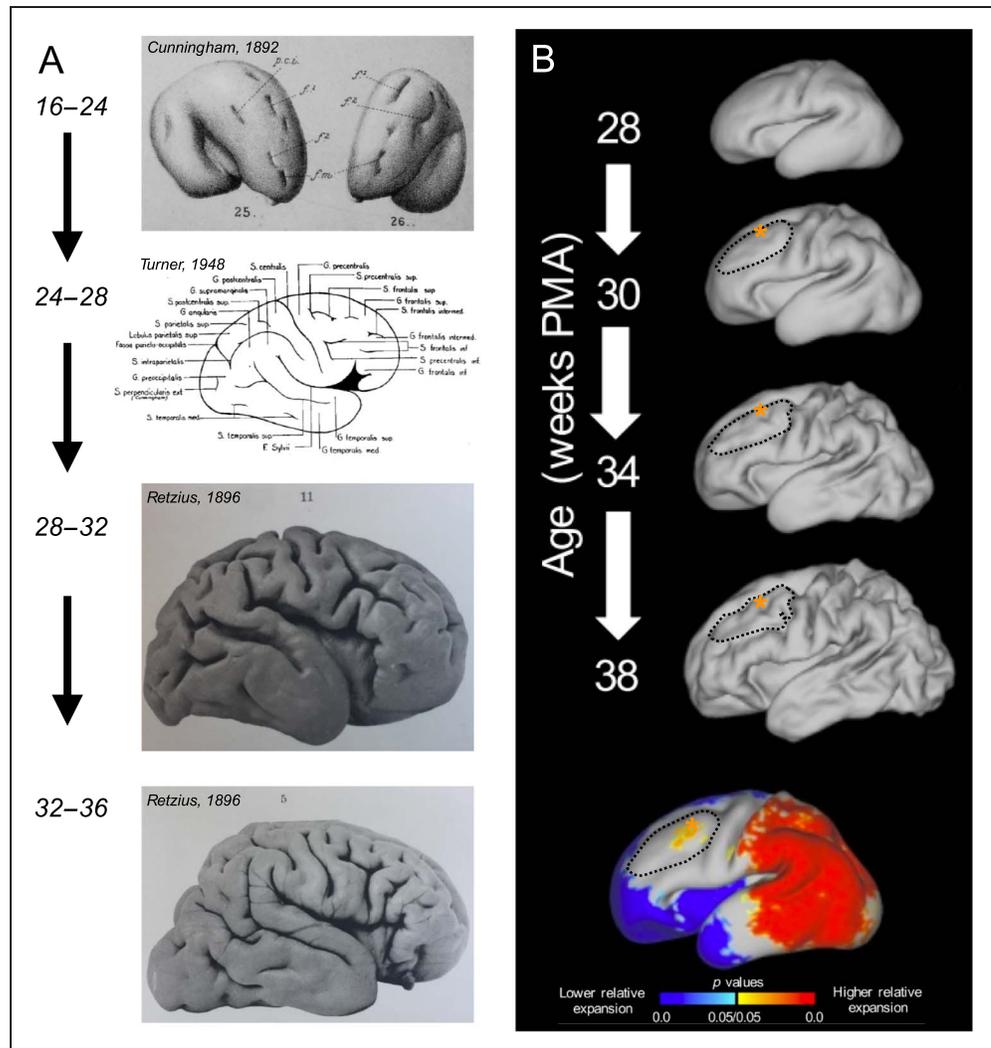
Despite these historical and modern issues contributing to our lack of understanding of tertiary sulci within LPFC (Figure 2A; Appendix), classic and modern studies seem to agree on the developmental trajectory of these sulcal components. That is, tertiary sulci emerge last in development, but not in a temporally uniform fashion across the cerebral cortex (Welker, 1990; Chi et al., 1977). Instead, they emerge at different time points, depending on the lobe they are in and also their topological positioning within that lobe. For the MFG, classic anatomists agreed that the “frontomarginal” and “middle frontal” sulcal components emerged from anterior to posterior (Figure 3A; Appendix). Between 16 and 24 weeks, the most anterior frontomarginal components appear (Turner, 1948; Retzius, 1896; Cunningham, 1892), whereas between 24 and 36 weeks, the rest of the sulci emerge in the middle and posterior portions of the MFG, respectively.

With modern neuroimaging tools, the temporal emergence and continued development of tertiary sulci can be revisited. Recent findings examining the development of cortical folding in preterm infants using MRI shows feasibility of this comparison. As illustrated in Figure 3B, shallow tertiary sulci begin to emerge at 30 weeks and then deepen at 38 weeks. Additionally, the location in LPFC that expanded the most during fetal development was in the vicinity of the posterior component of the pmfs (Figure 3B, bottom), which is consistent with the developmental timeline from anterior (early) to posterior (late) identified by classic neuroanatomists. These findings provide new evidence for the developmental trajectory of macroanatomical structures in LPFC and suggest a link between cortical folding patterns and the cognitive abilities supported by LPFC. That is, just as prolonged myelination is a hallmark of association cortex development (Miller et al., 2012), tertiary sulcal development in LPFC may be an important marker for a complex array of genetic and environmental factors related to variations in human cognitive abilities.

## **TERTIARY SULCI IN COMPARATIVE NEUROANATOMY AND PRIMATE EVOLUTION**

Among primates, the level of cortical folding (or gyrification index) tracks with evolutionary complexity, suggesting that sulcal structures are at the bare minimum markers of primate evolution (Zilles, Palomero-Gallagher, & Amunts, 2013). Classic and recent research findings indicate that some primate species display tertiary sulci that are likely homologous to human tertiary sulci in these cortical expanses. For example, Amiez and colleagues compared the sulcal morphology of ventral medial PFC (vmPFC) using anatomical MRI from human, chimpanzee, baboon, and macaque brains. Across

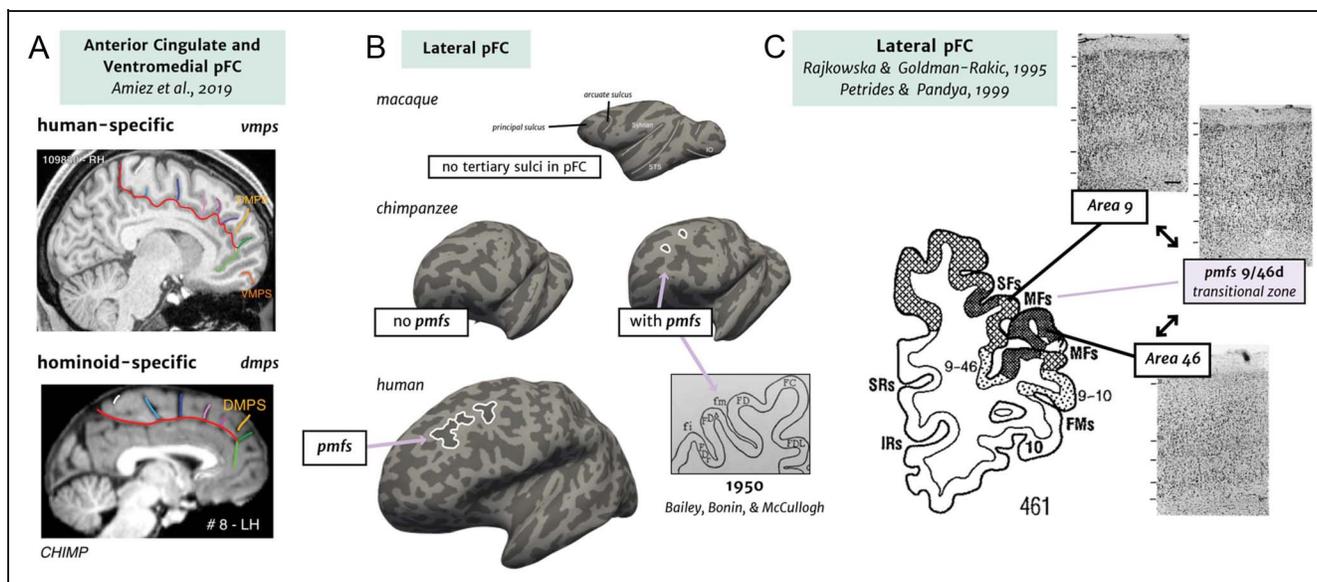
**Figure 3.** Sulci within the MFG likely emerge and develop along an anterior–posterior axis. (A) Top to bottom: Images from classic atlases and paper depicting the emergence of sulci during 16–24 weeks (Cunningham, 1892), 24–28 weeks (Turner, 1948), 28–32 weeks (Retzius, 1896), and 32–36 weeks (Retzius, 1896). Despite contentions regarding sulcal definitions within the MFG discussed in the main text and the Appendix, anatomists commonly agreed that sulci in the anterior MFG emerged first, whereas sulci in the posterior MFG emerged last in utero and continued to develop after birth (Appendix). (B) Top to bottom: MRI images depicting average cortical surfaces across preterm infants during different developmental time periods (PMA: postmenstrual age) in gestation (Garcia et al., 2018). Consistent with the classic images in (A) and as specified in the Appendix, tertiary sulci within the MFG become prominent during the seventh and eighth month in gestation. Black lines outline the MFG, and asterisks show correspondence with the approximate location of the posterior pmfs component (pmfs-p) based on the shading of the cortical surface. Bottom: An average cortical surface map comparing the relative expansion across development.



the four analyzed primate species, the majority of tertiary sulci in the vmPFC were only identifiable in “hominoids” (humans and chimpanzees), and a subset were human-specific (Figure 4A). For example, the dorsomedial polar sulcus (dmfs) was identified as a hominoid-specific marker present in most human brains and ~50% of chimpanzee brains, whereas the ventromedial polar sulcus was present in most individual human brains (64%) but entirely absent in chimpanzees and other primate brains. Interestingly, although the presence of major cytoarchitectonic areas is largely conserved across species in vmPFC, what are considered the most expanded areas (BA 9 and BA 10) were the locations for the identified tertiary sulci (Amiez et al., 2019).

In LPFC, consistent with Amiez and colleagues (2019), it is likely that some, but not all chimpanzees have all three pmfs components as in humans. Two different chimpanzee brains with and without tertiary sulci in the MFG are shown in Figure 4B, in contrast to an example human brain, in which tertiary sulci are always present within the MFG. Future studies performing morphological comparisons of tertiary sulci between chimpanzees and humans will further

quantify these observations. This homology may be important because the pmfs appears to delineate borders or transitional zones for cytoarchitectonic areas in both humans and chimpanzees. For example, the seminal papers of Rajkowska and Goldman-Rakic (1995a, 1995b) analyzed the cytoarchitecture of the LPFC within nine postmortem human brains. In the presented coronal sections of cytoarchitectonic Areas 9 and 46 (Figure 4C), a common trend appears that the pmfs (or “MFS,” as it was labeled) delineates a transitional zone between Areas 9 and 46 (Rajkowska & Goldman-Rakic, 1995a, 1995b). The characteristics of Areas 9 and 46 are different enough (Area 9 with a more prominent Layer 3, Area 46 with more prominent deeper layers) that Petrides coined Area 9/46d to describe this transitional zone (Petrides, 2005; Petrides & Pandya, 1999). We posit that this transitional zone is tightly coupled to the pmfs and may point to a mechanistic association between granular cortex and tertiary sulci in primates, with a specific expansion of middle cortical layers. For example, recent support for this hypothesis is evident from reexamining cytoarchitectonic studies of chimpanzees, showing that the pmfs also appears



**Figure 4.** Tertiary sulci across primate PFC. (A) The sulcal morphology of the medial PFC and ACC shown in example sagittal MRI sections of human and chimpanzee brains. The ventromedial polar sulcus (top) is a human-specific tertiary sulcus, whereas the dmps (bottom) is found in humans and over half of the chimpanzee hemispheres examined. Figure adapted from Amiez et al. (2019). (B) Top: Cortical surface (left hemisphere) from the NIH macaque brain template (<https://afni.nimh.nih.gov/NMT>) in which the principal and arcuate sulci are labeled. Middle: Two chimpanzee cortical surface reconstructions showing variability in the presence or absence of a pmfs (outlined in white) within the MFG (National Chimpanzee Brain Resource: <https://www.chimpanzeebrain.org/>; Hopkins, Li, Crow, & Roberts, 2017; Keller, Roberts, & Hopkins, 2009). The inset shows the pmfs (then labeled as “fm”) as the boundary between areas FD and FDΔ (adapted from Bailey et al., 1950). Bottom: An example human left hemisphere cortical surface reconstruction in which the prominent three pmfs components are outlined in white. (C) Schematic of a postmortem coronal section with the pmfs (labeled then as the middle frontal sulcus, MFs) indicating a transitional zone between cytoarchitectonic Areas 9 and 46. Inlets show Nissl-stained histological sections revealing the cytoarchitectural organization in Areas 9 and 46 and transitional Area 9/46d. Figures adapted from Rajkowska and Goldman-Rakic (1995a, 1995b) and Petrides and Pandya (1999). Additionally, a recent cytoarchitectonic atlas shows that the pmfs identifies a transition between 9/46v and 9/46d (Petrides, 2019).

to mark cytoarchitectonic transitions between granular regions FD and FDΔ in chimpanzee brains differing in the extent of granular cell proliferation in Layer 3 (Bailey & von Bonin, 1951; Bailey et al., 1950). These observations suggest that tertiary sulci could serve as an organizing framework to study PFC evolution and to compare with the evolution of cytoarchitecture and connectivity patterns across species. They further lead to potential mechanistic links relating tertiary sulci to the expansion of granular cortex and white matter across primate evolution (García-Cabezas, Zikopoulos, & Barbas, 2019; Van Essen et al., 2019; Donahue, Glasser, Preuss, Rilling, & Van Essen, 2018).

As tertiary sulci are identified as important landmarks in functional areas, especially within association cortices in humans, comparing tertiary sulci among primate species also leads to questions about whether sulci would serve as trait-level behavioral markers within and across species. Is variability in sulcal morphology in macaques, baboons, and chimpanzees associated with behavioral traits? Do animals with more “human-like” sulcal morphology (e.g., a chimpanzee with a dmps or pmfs) exhibit cognitive control or other behaviors closer to human-level performance? As more cognitive paradigms from the human literature are adapted for nonhuman primates (Badre, Frank, & Moore, 2015), these anatomical-behavioral relationships can begin to shed light on PFC structural-functional relationships across evolutionary timescales.

### TERTIARY SULCI AS MARKERS OF STRUCTURAL-FUNCTIONAL RELATIONSHIPS IN PFC: NETWORK INSIGHT FROM NEUROANATOMICAL PRECISION

One of Stuss’ research goals was to understand brain networks from improved neuroanatomical precision in lesion-behavioral studies. Many of Stuss’ studies examined the relationship between neuroanatomical damage and behavioral performance to determine brain-behavioral relationships (Stuss, 2011; Stuss & Levine, 2002; Stuss & Alexander, 2000). For these studies, Stuss and colleagues generated methods (Stuss et al., 2005; Stuss & Levine, 2002) to examine lesion location relative to cytoarchitectonic parcellations of cortex beyond Brodmann—specifically from Petrides and Pandya (1994). Such an approach not only provided cytoarchitectonic links to the lesion location but also functional properties of that cytoarchitectonic region. As Stuss writes,

The location of the lesions provides the clues to dissociating processes. (Stuss, 2011, p. 760)

Often, if a researcher strives for improved anatomical detail regarding either the cortical location of a lesion or a functional region (or both), it is assumed that the researcher favors a modular versus distributed theory of how information is represented in cortex. Or, that improved

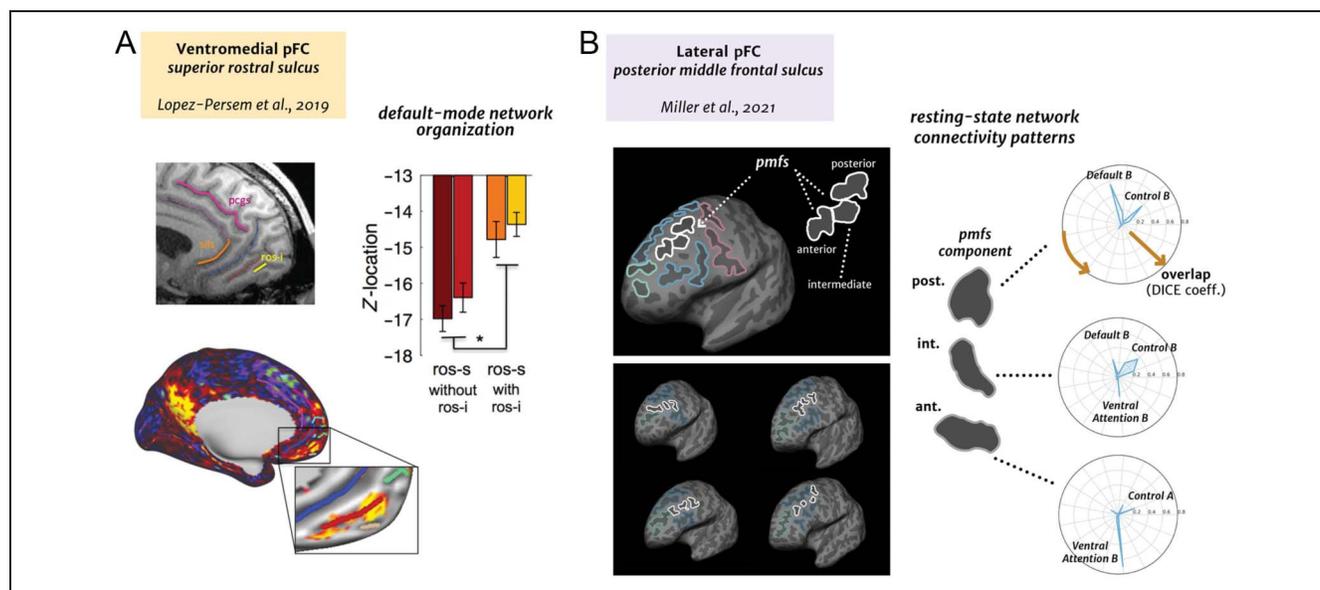
anatomical insight in general is just a type of “modern phrenology,” without relation to fundamental properties of neuronal functioning. On the contrary, Stuss was very clear about how his approach was a preliminary attempt to use improved anatomical precision in lesion research to gain insight into functional brain networks. Stuss wrote,

Our research on the effect of focal frontal lobe lesions on separable cognitive and noncognitive processes revealed distinct roles for different regions of the frontal lobes. Careful reading of the results leads to the conclusion that this is not a modern phrenology but a preliminary effort in the use of lesion research to understand integrated neural networks. Converging evidence from multiple methodologies compellingly argues for the regulatory role of the frontal lobes in networks involving posterior regions. (Stuss et al., 2002, pp. 400–401)

We echo Stuss’ clarity and emphasize that zooming in to tertiary sulci in PFC forms a foundation for understanding how these largely overlooked neuroanatomical structures contribute to typical brain function and cognition. Using modern multimodal neuroimaging datasets, two recent parallel lines of work show that meticulously labeling tertiary sulci within individuals uncovers new structural–functional relationships within PFC at the network level. In a recent study, the sulcal morphology of the vmPFC was carefully divided into four distinct patterns across individuals and the superior rostral sulcus, a tertiary sulcus, was found to colocalize with a hub of the default mode network (Lopez-Persem, Verhagen, Amiez, Petrides, & Sallet, 2019).

Furthermore, the presence or absence of nearby tertiary sulci shifted the functional organization within vmPFC. For example, the presence or absence of the tertiary inferior rostral sulcus (ros-i) shifted the location of the vmPFC peak of the default mode network superiorly (Figure 5A). Moreover, individual differences showed higher connectivity strength of the vmPFC with the rest of the default-mode network in individuals with an ros-i (64.04%) compared with those without an ros-i. These results indicate a relationship between sulcal variability and functional variability within vmPFC as well as other cortical locations. For instance, the presence of the ros-i also resulted in a functional cluster in the posterior cingulate cortex that was not present in individuals lacking an ros-i.

A second line of modern neuroimaging evidence comes from our recent work characterizing the pmfs in LPFC. We applied a recently proposed labeling scheme of tertiary sulci in LPFC (Petrides, 2019) to test whether these sulci could be defined in the LPFC of individual participants *in vivo*. Consistent with Petrides’ (2019) proposal, we identified the pmfs as a prominent tertiary sulcal structure that consists of three distinct components along an anterior–posterior axis within each of 72 individual hemispheres. Although the pmfs was present within each individual, its location was the most variable across hemispheres of all sulci examined in LPFC. This variability likely contributed to the historical ambiguity of its identification (Figure 1) as well as to its disappearance in commonly used average cortical surfaces (Miller et al., 2021). To determine if pmfs components have distinct functional network organization, we analyzed multimodal data from the



**Figure 5.** Network insights from identifying tertiary sulci. (A) The superior rostral sulcus (ros-s) serves as a landmark for default-mode network connectivity strength and organization. Top left: Sulcal organization in vmPFC showing the ros-i. Bottom left: The location of peak functional connectivity to the default-mode network within the vmPFC is consistently highest at the anterior tip of the ros-s. Right: Individuals with versus without an ros-i show a shift in the peak location of default-mode network connectivity in the vmPFC. Specifically, both the peak location of default-mode network connectivity and the ros-s are shifted superiorly when an ros-i is present. Figures adapted from Lopez-Persem et al. (2019). (B) Left: The three components of the pmfs in the MFG outlined in white on five individual cortical surfaces (left hemispheres). Right: The three pmfs components exhibit different patterns of network connectivity along an anterior-posterior gradient. Modified with permission from Miller et al. (2021).

Human Connectome Project (HCP) after manual labeling of sulci in LPFC. The three pmfs components were dissociable based on myelin content, resting-state functional connectivity profiles, and task activations across a meta-analysis of 83 cognitive tasks (Figure 5B). Together, these results show that each pmfs component has a different network fingerprint (Figure 5B).

In combination with recent findings, these results show the utility of using tertiary sulci to study functional organization and properties at the level of areas and networks in the cerebral cortex (Weiner et al., 2014, 2018; Lorenz et al., 2017; Amiez et al., 2006, 2013; Amiez & Petrides, 2009). Because tertiary sulci are prominent within individuals, they can serve as a scaffolding to link microanatomical and functional features of the cerebral cortex (Weiner, 2019; Weiner et al., 2014, 2018), as well as allow for communication and replication between research groups that is more accurate than average cortical surface reconstructions or stereotaxic coordinates. In terms of the latter, depending on the cortical expanse, tertiary sulci can nearly disappear entirely on average cortical surface templates, which is a direct consequence of their variability when aligned to stereotaxic space (Miller et al., 2021; Weiner et al., 2014). As such, average  $x, y, z$  stereotaxic coordinates likely will not accurately predict the location of tertiary sulci as previously shown (Weiner et al., 2014). Instead, until computational methods are developed to precisely identify tertiary sulci automatically (expanded further in the next section), the manual definition of tertiary sulci within each individual participant will continue to serve as a personalized coordinate system for each individual that is also generalizable across individuals. That is, “personalized” in the sense that the location (or coordinates) of tertiary sulci will likely be specific to that individual and “generalizable” in the sense that once tertiary sulci are defined in a given hemisphere, sulcal–functional or sulcal–behavioral relationships can be compared among many individuals rather than relying on coordinates that miss the location of small, shallow tertiary sulci entirely. Once precisely defined, individual differences in the morphology of tertiary sulci within and across individuals can then be leveraged to discover important relationships with the functional properties of cortical areas and, ultimately, a host of cognitive processes. For example, across individuals, tertiary sulci show extensive individual differences in depth, length, shape, and location (Miller et al., 2020, 2021; Borne, Rivière, Mancip, & Mangin, 2020; Amiez et al., 2019; Lopez-Persem et al., 2019; Weiner, 2019; Weiner & Zilles, 2016; Garrison et al., 2015; Weiner et al., 2014; Paus et al., 1996; Armstrong et al., 1995; Welker, 1990; Chi et al., 1977; Sanides, 1962, 1964; Bailey & von Bonin, 1951; Bailey et al., 1950; Connolly, 1950; Turner, 1948; Retzius, 1896; Cunningham, 1892). Often this variability corresponds with functional and/or microanatomical organization in the cerebral cortex or behavioral performance. For instance, tertiary sulcal morphology in ventral temporal cortex predicts the delineation of functional and microarchitectonic boundaries (Weiner, 2019; Weiner & Zilles, 2016; Grill-Spector

& Weiner, 2014; Weiner et al., 2014) and even perceptual abilities across individuals (Parker et al., 2020). Additionally, (i) medial PFC and cingulate areas also show distinct functional organization based on the presence of certain tertiary sulci (Figure 5), and (ii) recent studies show that individual differences in sulcal morphology in PFC are related to individual differences in cognition (Voorhies, Miller, Yao, Bunge, & Weiner, 2020; Amiez, Wilson, & Procyk, 2018; Brun et al., 2016).

These findings also lead to new questions regarding the emergence of tertiary sulci and the development of anatomical and functional cortical connectivity patterns across individuals. For example, does the emergence of the ros-i in development precede the detection of a default mode network? Promising new lines of infant fMRI scanning may be able to reveal how the developmental trajectory of tertiary sulci in gestation relates to the layout and functioning of whole-brain functional networks (Ellis & Turk-Browne, 2018). Long-range (Schilling et al., 2018; Van Essen et al., 2014; Welker, 1990) and short-range (Reveley et al., 2015) connectivity differ between gyri and sulci, and early-life anatomical and functional data open a new array of research tools and questions for structural–functional relationships in PFC.

### **TERTIARY SULCI AS LANDMARKS IN ASSOCIATION CORTICES: UNRESOLVED THEORETICAL PERSPECTIVES AND FUTURE DIRECTIONS**

The potential importance of tertiary sulci as landmarks in human association cortices was championed by Vogt and Vogt (1919) and further refined by Sanides (1962, 1964). Sanides proposed “gradations” or “streams,” which matched the directions of neocortical development during brain evolution (Henssen et al., 2016; Sanides, 1964). Consistent with observations by Vogt and Vogt, Sanides noted that tertiary sulci often served as boundaries for cortical gradations in the myeloarchitecture of PFC sections (for a detailed description of Sanides’ methods and ideas, see Henssen et al., 2016).

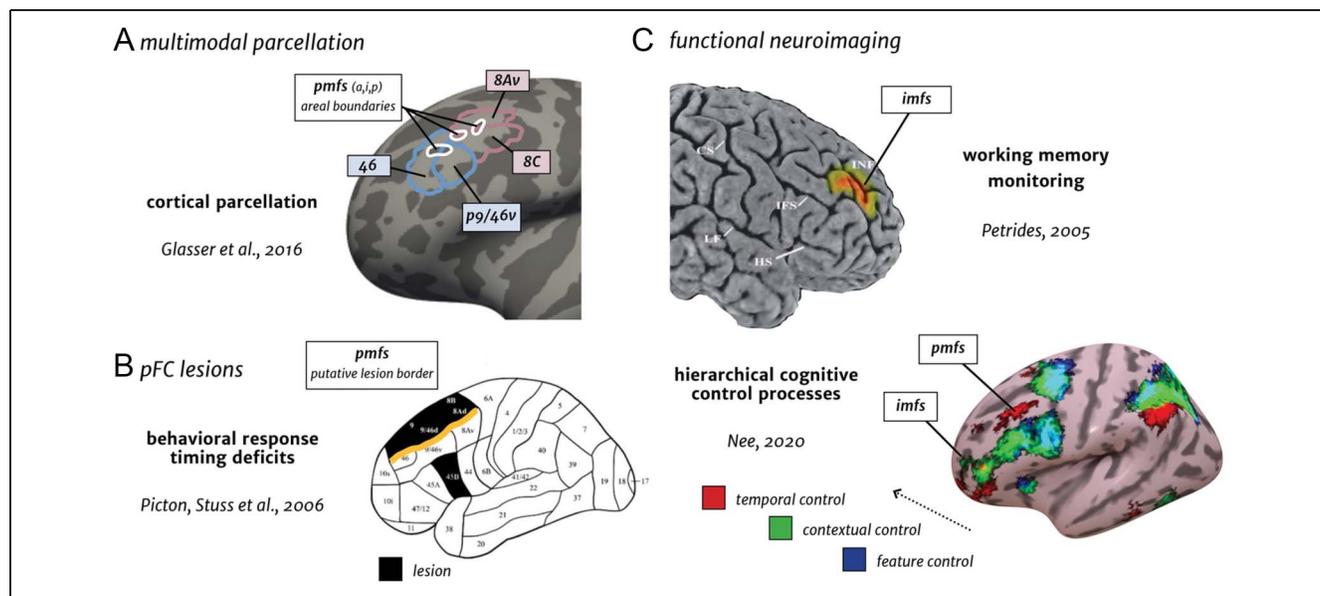
More recent work in the functional neuroimaging and neurology literature seem to also support this correspondence. For example, examining the relationship between the pmfs components and the recent whole-brain multimodal parcellation from Glasser and colleagues (2016) suggests that (1) the pmfs-p and pmfs-i likely identify boundaries between Area 8Av superiorly from Area 8C inferiorly, (2) the pmfs-i likely identifies a boundary between a posterior cluster containing Areas 8Av and 8C and a more anterior cluster containing Areas 46 and p9/46v, and (3) the pmfs-a likely identifies the boundary between Areas 46 and p9/46v. As this is a parcellation derived from averaging brain data across individuals, future studies can explore if tertiary sulci correspond to transitions between multimodal areas in individual participants.

Additionally, identifying the location of the pmfs components in previously published images from Stuss’ work

shows that lesions superior to these components likely result in response time deficits (Figure 6, left). Functional and behavioral links are not limited to the location of pmfs components, but also other nearby sulci in LPFC. For instance, the intermediate frontal sulcus, which is anterior to the pmfs, seems to identify a functional activation for the monitoring (or manipulation) of working memory content (Amiez & Petrides, 2007; Figure 6, right). Finally, a functional region preferentially activated during higher order, temporal control appears to colocalize with the three pmfs components, whereas the intermediate frontal sulcus seems to colocalize with a functional region preferentially activated during contextual control (Nee, 2020; Nee & D'Esposito, 2016). The combination of these interpretations of previously published data demonstrates the utility of tertiary sulci to situate functional maps across findings from different research groups and to ground functional maps to evolutionary new anatomical features of the cerebral cortex.

When considering these anatomical–functional correspondences in the context of future research, it is important to also consider the limitations of examining the functional role of tertiary sulcal patterns and individual differences in (i) any portion of the cerebral cortex and (ii) any relevant behavior or cognitive process associated

with a given cortical expanse. The main limitation is that there is often no causal inference when examining the anatomical–functional relationship between tertiary sulci and functional regions (Figure 5). Nevertheless, previous research in ventral temporal cortex does show a causal relationship among the location of functional regions relative to tertiary sulci and perception (Schrouff et al., 2020; Rangarajan et al., 2014; Parvizi et al., 2012). Thus, an immediate open question is whether the anatomical–functional relationships emphasized here for PFC also have causal implications, which can be addressed in future research. Additionally, as cortical morphology changes with age, it would be especially useful for future studies to quantify how much unique variance is explained by morphological features of tertiary sulci above and beyond age, as well as over and beyond other aspects of gyrification that change with age, such as cortical thickness. Ongoing work in a developmental cohort using a model-based approach does just this and shows that the depths of a subset of tertiary LPFC sulci explain reasoning ability in both discovery and replication cohorts above and beyond age, as well as beyond the variance explained by cortical thickness (Voorhies et al., 2020). Thus, ongoing work suggests that considering tertiary sulcal morphology explains cognition well beyond incremental predictive validity in LPFC.



**Figure 6.** Tertiary sulci are useful for building an understanding of LPFC across scales of organization. (A) Maximum probability maps (thresholded at 33% overlap across participants; white outlines) for the pmfs-p, pmfs-i, and pmfs-a on the FreeSurfer average template (left hemisphere) relative to four areas from a multimodal cortical parcellation based on structural and functional MRI data (Glasser et al., 2016). If and how the different pmfs components serve as areal boundaries in individual participants can be tested in future research. Modified with permission from Miller et al. (2021). (B) A schematic illustration of a lateral view of a left hemisphere from Picton, Stuss, Shallice, Alexander, and Gillingham (2006). The location of lesions that produced a significant ( $p < .05$ ) deterioration in behavioral performance are illustrated in black. Yellow: Approximate location of the three pmfs components discussed in this paper that could serve as putative lesion borders. (C) Top: Although we emphasize pmfs components in this paper, we recognize that identifying other sulci in individual participants could also provide anatomical–functional insight. For example, previous work indicates that the intermediate frontal sulcus (ifms) colocalizes with a functional region that is crucial for monitoring during working memory. Bottom: Recent research at the group level (Nee, 2020; Nee & D'Esposito, 2016) indicates that pmfs components likely couple with functional activations associated with temporal control, whereas functional activations associated with contextual control likely couple with the ifms—both of which can be tested further at the level of individual participants in future studies. Altogether, future research can examine if/how tertiary sulci serve as relevant boundaries, or landmarks, across scales of LPFC organization. Figures adapted from listed studies.

Future work in freely available, large, multimodal datasets such as the HCP and U.K. BioBank are needed to systematically relate variability in these tertiary sulci to a wider array of cognitive domains. Nevertheless, increasing evidence from classic and recent studies suggests that some tertiary sulci serve as landmarks that bridge spatial scales (microns to networks), modalities (functional connectivity to behavior), and even species.

In addition to this ongoing and future work, we emphasize that examining the relationship between tertiary sulci and other types of data presently requires accurate, validated, and manually defined sulci in individual participants. For example, in our work, we manually defined 936 sulci in 72 hemispheres. Although 72 is a large sample size compared with other labor-intensive anatomical studies in which 20 hemispheres were considered sufficient to encapsulate individual differences (Amunts & Zilles, 2015), 2400 hemispheres are available just from the HCP dataset alone (Glasser et al., 2013). Defining tertiary sulci in only the LPFC of every HCP participant would require ~26,400 manual definitions, whereas defining all tertiary sulci in the entire HCP dataset would require over a quarter of a million (~256,800) manual definitions. Consequently, manual identification of tertiary sulci will continue to limit sample sizes until new automated methods are generated. Uncovering structural–functional relationships in PFC will be advanced by leveraging anatomical expertise to develop computational approaches to neuroanatomy, such as deep learning algorithms. Indeed, recent work using deep learning algorithms and expanded training shows improvements in the ability to identify tertiary sulci automatically in LPFC (Lyu et al., 2021; Borne et al., 2020; Klein et al., 2017). As such, it is most likely that LPFC tertiary sulci can “survive” normalization of individual brain images given these advanced computational techniques. This work is especially important as individual-level data have been increasingly recognized as important for basic and clinical human

research, in which it is critical to understand within-participant native anatomy, function, and behavior (Seitzman et al., 2019; Fisher, Medaglia, & Jeronimus, 2018; Gordon et al., 2017; Stuss, 2016).

## CONCLUDING REMARKS

Motivated by Stuss’ provocative concept of considering PFC as a “cognitive globe,” we have discussed classic and recent findings regarding the development, evolution, function, and cognitive role of PFC tertiary sulci with a particular focus on vmPFC and LPFC. Tertiary sulci are situated in a unique position within the complexity of this cognitive globe as they are the smallest and shallowest of sulci in PFC, yet can offer insights that bridge spatial scales (microns to networks), modalities (functional connectivity to behavior), and species. The unique position of tertiary sulci generates innumerable open questions, some that we have included in the main text and five of which we highlight in Box 1. Future research will continue to shed light on the unique position of tertiary sulci not only in PFC but also in other association cortices.

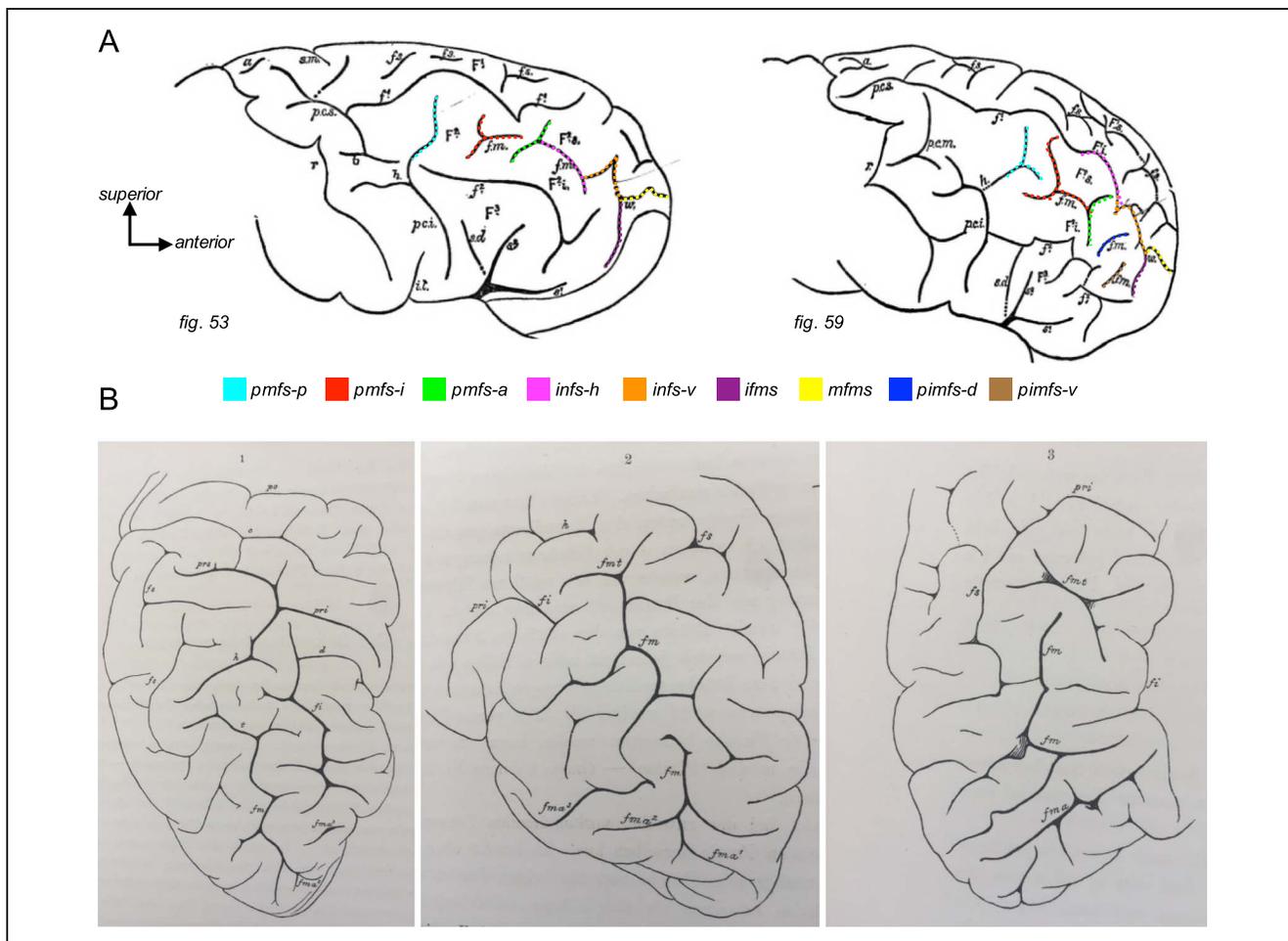
## APPENDIX: HISTORICAL CONTEXT FOR AMBIGUITY OF SULCAL LABELING IN THE MIDDLE FRONTAL GYRUS

Despite contentions regarding definitions and labels for the middle frontal sulcus throughout history, there have been three consistent themes regarding the sulcal patterning of this sulcus: (1) Although classic anatomists credited Eberstaller for labeling the middle frontal sulcus in 1890 (Figure A.1), they also acknowledged Hervé (1888) for first describing it and ascribing its importance; (2) There are extensive individual differences in the patterning of the middle frontal sulcus across individuals, which has

### Open questions

- How many of the ~75 tertiary sulci in the human cerebral cortex serve as anatomical, functional, or multimodal landmarks?
- How does the emergence of tertiary sulci in development relate to the development of functional networks?
- Is there a relationship between the expansion of granular cortex and tertiary sulci?
- Can tertiary sulci serve as individual-level biomarkers in cognitive and behavioral disorders?
- In order to accurately define tertiary sulci in large datasets ( $n = 1,000+$ ), can learning algorithms be developed to automatically define tertiary sulci within individual hemispheres with a level of precision that approaches manual definitions?

**Box 1.** Open questions for future investigations regarding tertiary sulci and the anatomical and functional organization of PFC and other association cortices.



**Figure A.1.** Revisiting classic schematic depictions of the middle frontal sulcus with a modern lens. (A) Two schematics from Cunningham (1892). Dotted lines indicate modern definitions of sulci in LPFC (see legend). Though several sulci were either unlabeled or had the same label (fm) in Cunningham's original illustrations, each schematic fits the modern definition of LPFC sulci proposed by Petrides (2019) and studied in our recent work (Miller et al., 2021). Figure numbers refer to those in Cunningham's original work found here: <https://archive.org/details/cu31924032226668/>. (B) As discussed in the Appendix, despite historical contentions regarding the middle frontal sulcus, anatomists commonly acknowledged the fractionated nature of this sulcus and the common presence of a transverse component in the posterior MFG. This component was so common that Retzius (1896) labeled it as fmt (middle, right) or t (left) in schematics depicting LPFC sulcal patterning in his 1896 atlas. This component is consistent with the modern definition of the pmfs-p.

led lumping sulcal components together as one sulcus or splitting each sulcal component as a separate label; and (3) Despite contentions, classic anatomists largely agreed that the sulci within the MFG emerge in gestation along an anterior to posterior axis. We consider each of these points below and include classic quotations and images when appropriate.

1. Classic anatomists commonly credit Hervé (1888) for first describing the middle frontal sulcus. Four (nonexhaustive) examples are included below in chronological order, with footnotes that include links to the larger text from which the quotation was taken should the reader be interested in exploring further:
  - a. Eberstaller has the credit of having first clearly recognized and described this fissure, although it would seem that it was also independently identified as a distinct fissural integer by Hervé. It is one of great

interest, but in the hands of these two authors it has been assigned, as we shall see later on, an altogether undue importance. (Cunningham, 1892, p. 264)<sup>2</sup>

- b. I may not omit adding a few words concerning the s. frontalis. medius. This sulcus, though already alluded to by Hervé (1888), was first fully described by Eberstaller (1890) and soon after him amply discussed by Cunningham (1892). (Ariëns Kappers, 1929a, p. 307)<sup>3</sup>
- c. *FRONTALIS MEDIUS*. Hervé (1888) and Eberstaller (1890) regarded the frontal medius sulcus (fm) as homologous with the s. rectus of the lower primates. This seems to be true only of the sagittal part caudal to the bifurcation, if the s. rectus, as above stated, is homologous with the fronto-marginal. The greater part of the midfrontal appears, however, to be a new sulcus accompanying the expansion of the frontal association area...in well developed frontal

lobes it takes on the importance that Hervé and Eberstaller assigned to it. (Connolly, 1950, p. 197)<sup>4</sup>

d. Within the middle frontal gyrus there is frequently a fairly long middle frontal sulcus (fm), roughly parallel to superior and inferior frontal sulci. This sulcus was considered as an important separate entity by Hervé (1888) and Eberstaller (1890). The latter described it as a sagittal furrow, beginning with a transverse bifurcation at about the middle between precentral gyrus and orbital margin, and ending frequently (see Table 13) near the orbitodorsal margin in a similar bifurcation, evidently a part of Wernicke's frontomarginal sulcus. Most subsequent observers (Cunningham, Retzius, Connolly, Shellshear, Kononova, etc.) commented on the great variability of this sulcus. (Bailey & von Bonin, 1951, p. 44)<sup>5</sup>

2. There are extensive individual differences in the definition of the middle frontal sulcus across individuals, which is exacerbated with postmortem material (Miller et al., 2021). Cunningham was bewildered by this variability as indicated in his 1892 atlas:

The degree of variability of this sulcus, as established by this method, is very bewildering... a sulcus which assumes so many different forms is not likely to be one of such leading and conspicuous morphological value as Eberstaller and Hervé would have us believe. (Cunningham, 1892, p. 265)

Additionally, although anatomists could often identify the middle frontal sulcus as described by Hervé, Eberstaller, and others, like Cunningham, they often referred to the extensive variability in its appearance. For example, Connolly (1950) writes,

Good examples illustrating Eberstaller's description are found in our material. But there is every gradation between what is hardly more than a short stem of the fronto-marginal and a highly developed and important sulcus. (Connolly, 1950, p. 197)<sup>6</sup>

When confronted with this variability, anatomists had variable strategies. For example, in 37 figures (a majority of which are hand-drawn schematics), Shellshear (1937) recognized five different groups of the sulcus frontalis medius: (i) The sulcus frontalis medius is in one piece running from its posterior transverse element to the sulcus frontomarginalis. (ii) The posterior part of the sulcus frontalis medius is separate; the anterior part is confluent with the sulcus frontomarginalis. (iii) The two parts of the sulcus frontalis medius (proper) are confluent; the sulcus frontomarginalis is separate. (iv) The two parts of the sulcus frontalis medius and the sulcus frontomarginalis are all separate from one another. (v) A heterogeneous group. Regarding the latter, Shellshear writes,

It is difficult to recognize with certainty the various sulci and it seems better, therefore, to record the

group pictorially for future use. (Shellshear, 1937, p. 398)<sup>7</sup>

Of the five groups defined by Shellshear, the most common strategy was to acknowledge a posterior transverse component that was commonly separated from other components of the middle frontal sulcus. Topologically—relative to other sulci—this component is in a similar location as the modern definition of the pmfs-p. In Cunningham's (1892) atlas, he described that Eberstaller referred to this transverse component (though Eberstaller did not label this component in his schematic; Figure 1). Cunningham wrote:

Eberstaller has referred to a small transverse branch with which its hinder end is in continuity. When this is the case (fig. 53, *f.m.*, p. 248), it will be noticed that a deep annectant gyrus always intervenes, and prevents a free union between the two; indeed, in the majority of cases the annectant gyrus is on the surface and the transverse furrow is thus completely cut off from the sagittal portion of the middle frontal sulcus. A second transverse furrow, behind that already mentioned, is also almost invariably present, and a union between the two is by no means uncommon (fig 59, *f.m.*, p. 262). These small furrows undoubtedly belong to the same system as the portion of the sulcus described by Eberstaller. They prolong it backwards, and bring it into close association with the horizontal part of the inferior praecentral sulcus. They are intermediate links, as it were, and the truth of this is to be seen in those rare cases where they are not only joined to each other, but also to the portion of the middle frontal furrow which lies in front of them, and to the horizontal part of the inferior praecentral sulcus which lies behind them. (Cunningham, 1892, pp. 265–266)

Consistent with our recent findings regarding the shallowness of the pmfs and multiple components of the pmfs (Miller et al., 2021), Cunningham further wrote:

As a general rule I have found it shallower than either the second or first frontal furrows. In a large proportion of cases it is interrupted by one or two deep annectant gyri. These may appear at different places, but as a rule, one is situated mid-way between its two extremities, whilst the other is placed at its junction with its anterior terminal cross-piece. It is not very uncommon to find one or both of these annectant gyri on the surface, thus breaking up the furrow into separate pieces. When this occurs, the isolated portions of the sulcus tend to assume a more or less transverse direction. Taking into consideration, then, the two pieces of the furrow which lie in front of the horizontal part of the inferior praecentral furrow, it is possible to imagine a hemisphere in which the sulcus frontalis medius is represented by five completely separate

portions. I have not met with such a condition...In eight hemispheres, however, I have observed the sulcus in four pieces. (Cunningham, 1892, p. 266)

Consistent with modern definitions of pmfs components, Cunningham further explained that Hervé (1888) acknowledged the presence of the middle frontal sulcus as a series of isolated furrows.<sup>8</sup> In addition to Hervé, Eberstaller, and Cunningham, other anatomists often acknowledged a separate transverse component in the vicinity of the modern pmfs-p. For example, using postmortem brains, Retzius (1896) referred to this component as *fmt* (Figure A.1), whereas Ariëns Kappers used endocasts of human skulls, as well as postmortem brains and a number system to label sulcal components in the MFG. 8 in his system referred to the intermediate fossa (Ariëns Kappers, 1928, 1929a, 1929b) in a similar location as pmfs-i, whereas 6' and 7c were in locations similar to pmfs-p and pmfs-a, respectively.

Taken together, although classic anatomists acknowledged the extensive variability of the middle frontal sulcus, they also commonly acknowledged the fact that it comprised several different components. Although many of them had different strategies regarding whether to identify these components with distinct labels, it was common to acknowledge a posterior transverse component whose macroanatomical and topological location relative to surrounding sulci is similar to the modern definition of the pmfs-p.

3. Despite contentions among classic anatomists regarding how to define and label sulci within the MFG, there was common agreement that sulci within the MFG emerged in gestation along an anterior to posterior axis and, additionally, that the posterior components have a prolonged development after birth. For example, Ariëns Kappers (1929a) referenced Hervé's documentation of developmental differences between anterior portions of this sulcus and more posterior "fissurets." Ariëns Kappers wrote:

HERVÉ, struck by the early appearance of the frontal half of this sulcus, believes that its breaking up into transverse fissurets in adults is due to a strong development of the region in which it occurs. (Ariëns Kappers, 1929a, p. 308)

Consistent with Hervé's observations, Cunningham also documented the early emergence of the frontomarginal and anterior middle frontal sulcal components in fetal brains compared with the late emergence of the posterior components. Cunningham writes,

Hervé claims for the sulcus frontalis medius a precedence over the other frontal furrows which it does not deserve. He states that it appears in the sixth month, and asserts that it is "le sillon primitif," which divides "the frontal lobe into two stages, or lobules, previous to its decomposition into convolutions." It is true that in a few instances I

have observed the sulcus frontalis medius in the cerebrum of a sixth month foetus, and I have figured what seems to me to be four examples of this (Pl. II., figs. 22, 23, 25, 26), but in each of these cases, with one exception, it is associated with the other frontal sulci. This early development of the sulcus medius is quite exceptional. As a general rule it does not appear until about the middle of the seventh month. The anterior sagittal stem is first formed. In figure 63, p. 276, it will be seen as a short continuous furrow; but in figure 62, p. 274, it is merely represented by two pit-like depressions. Its two posterior parts come into existence later, and may either remain distinct as two separate transverse furrows, or establish a superficial connection with each other and the main stem (fig. 54, p. 250, and fig. 60, p. 268). (Cunningham, 1892, p. 278)

Building on these previous observations, Turner (1948) considered three developmental stages in his study of the cerebral cortical pattern: (1) late intrauterine (fetal age of 7 months and birth), (2) early postuterine (birth and 2 years), and (3) late postuterine (2 years and adult life [20 years old]). Referring to the pmfs as the sulcus frontalis intermedius (after Ariëns Kappers), Turner detailed this developmental progression from anterior to posterior during these three different stages. Turner (1948) writes:

- a. Late intrauterine:

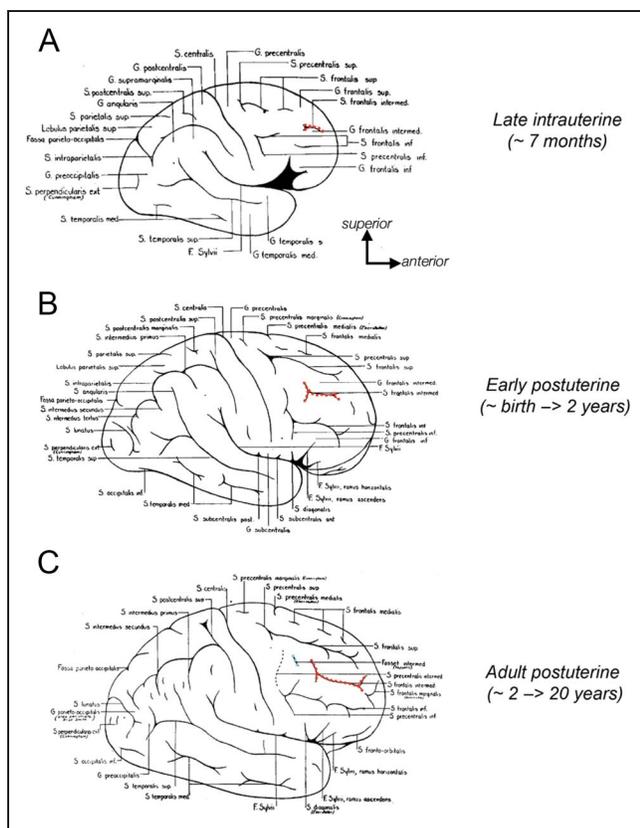
Within this rapidly growing area, and near the frontal pole, is a small horizontal sulcus, the commencement of the sulcus frontalis intermedius. At this stage it has a forward extension, which is directed downward and terminates posteriorly in a division of small size. (Turner, 1948, p. 2)

- b. Early postuterine:

The sulcus frontalis intermedius is now more extensive than it was previously. Its posterior branching termination has developed into an almost vertically placed sulcus, owing probably to the development of the cortex immediately behind it (motor area). The anterior, downwardly directed extension of the former stage is now subdivided. (Turner, 1948, p. 3)

- c. Late postuterine:

The sulcus frontalis superior and the sulcus frontalis inferior (primus and secundus of Cunningham) are both elongated and both connected with the corresponding precentral sulci. Each has numerous branches. Between them lies a greatly extended sulcus frontalis intermedius, which has a definite transverse tail at each extremity. The small, isolated sulci between this and the frontal pole have increased in number. The sulcus frontalis medialis has extended in length and its portions never join to form a single running sulcus. (Turner, 1948, pp. 4-5)



**Figure A.2.** Sulci within the MFG likely emerge and develop along an anterior–posterior axis. As described in the Appendix, Hervé (1888), Cunningham (1892), Retzius (1896), Turner (1948), and likely others commonly proposed that sulci within the MFG emerged along an anterior–posterior axis. Turner (1948) schematically illustrated this progression clearly in his study of three developmental stages of the cerebral cortical pattern. (A) Late intrauterine (fetal age of 7 months and birth). (B) Early postuterine (birth and 2 years). (C) Late postuterine (2 years and adult life [20 years old]). Referring to the sulcus frontalis intermedius (after Ariëns Kappers), the reader can appreciate that this sulcus extends more posteriorly with each stage (from A through C). In the last stage, the reader can also appreciate the emergence of the “fosset intermedius” (cyan), which is in a consistent location as Retzius’ *fms* and the modern *pmfs-p*.

A subset of Turner’s (1948) and Cunningham’s (1892) developmental observations are depicted in Figure 2 and Figure A.2. Taken together, despite historical contention regarding the definition and labeling of sulci within the MFG, anatomists examining the emergence of these sulci in gestation and after birth largely agreed that those in the anterior MFG emerged first, whereas those in the posterior MFG emerged last. This emergent trajectory nicely aligns with modern neuroimaging measurements (Figure 3), as well as motivates a number of open questions for future research (Figure 6 and Box).

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## Diversity in Citation Practices

A retrospective analysis of the citations in every article published in this journal from 2010 to 2020 has revealed a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were  $M(an)/M = .408$ ,  $W(oman)/M = .335$ ,  $M/W = .108$ , and  $W/W = .149$ , the comparable proportions for the articles that these authorship teams cited were  $M/M = .579$ ,  $W/M = .243$ ,  $M/W = .102$ , and  $W/W = .076$  (Fulvio et al., *JoCN*, 33:1, pp. 3–7). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article’s gender citation balance. The authors of this article report its proportions of citations by gender category to be as follows:  $M/M = .714$ ,  $W/M = .114$ ,  $M/W = .129$ , and  $W/W = .043$ .

## Notes

1. Specifically, Stuss (2011) wrote: “There is no central executive. There are, instead, numerous domain general processes discretely distributed across several frontal regions that act in concert to accomplish control” (Stuss, 2011, p. 759).
2. Cunningham’s atlas is freely available at the following link: <https://archive.org/details/cu31924032226668/>.
3. This quote comes from a physical book that has not yet been digitized. As Ariëns Kappers includes a three-page addendum to his book regarding the middle frontal sulcus, including a historical summary up to that point, we will include it at the following link with the publication of this paper: [www.cognitiveneuroanatomy.com/Publications/](http://www.cognitiveneuroanatomy.com/Publications/).
4. Connolly’s atlas is freely available through Hathitrust: <https://catalog.hathitrust.org/Record/001576611>.
5. Bailey and von Bonin’s atlas is freely available at the following link: <https://archive.org/details/isocortexofman612bail>.
6. Connolly’s atlas is freely available through Hathitrust: <https://catalog.hathitrust.org/Record/001576611>.
7. Shellshear’s paper is available at the following link: <https://royalsocietypublishing.org/doi/pdf/10.1098/rstb.1937.0005>.
8. Cunningham included a direct quote from Hervé in French in which he writes: “Hervé has also recognized the interrupted form of the sulcus. He wrote: Mais sur un grand nombre de cerveaux, et non tous parmi les plus simples, la face convexe de  $F^2$  (i.e., middle frontal convolution) est par-courue en son milieu par une série d’incisures et de sillons isolés, quelque-fois continus, qui manifestement la dédoublent sur une partie plus ou moins notable de sa longueur en deux plis distinct” (Cunningham, 1892, p. 267).

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