

*Using tertiary sulci to map the “cognitive globe”
of prefrontal cortex*

Jacob A. Miller¹, Mark D’Esposito^{1,2}, Kevin S. Weiner^{1,2}

¹Helen Wills Neuroscience Institute, ²Department of Psychology,
University of California-Berkeley

Corresponding author:

Jacob A. Miller

jacob_miller@berkeley.edu

210 Barker Hall

University of California-Berkeley, Berkeley, CA, 94720

Keywords: prefrontal cortex, functional neuroanatomy, morphology, gradients, brain mapping, higher-order cognition

ABSTRACT

Stuss (1984) considered the human prefrontal cortex (PFC) as a “cognitive globe” 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 (MFG). 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 and LPFC. Fourth, we revisit and update unresolved theoretical perspectives considered by Vogt and Vogt (1919) and Sanides (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, 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, prefrontal cortex (PFC), which is disproportionately expanded in the human brain, is particularly important given its central role in cognitive control and goal-directed behavior (Donahue, Glasser, Preuss, Rilling, & Van Essen, 2018; E. K. Miller & Cohen, 2001; Stuss, 2011; Stuss & Alexander, 2000; Stuss & Knight, 2012). Throughout his career, Don Stuss used maps of lesion damage to begin parcellating the PFC into the component pieces of a “cognitive globe” as he described in the above quote (Stuss, 1984; Stuss, 2011; Stuss & Alexander, 2000; Stuss & Knight, 2012). In the decades since, functional maps and parcellations of the PFC 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; (Badre & D'Esposito, 2009; Demirtas et al., 2019; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007; Nee & D'Esposito, 2016; Reid et al., 2016). Additionally, several different anatomical, functional, and multimodal approaches have further parcellated PFC into dozens of different areas (Eickhoff, Yeo, & Genon, 2018; Glasser et al., 2016; Goulas, Uylings, & Stiers, 2012; Kong et al., 2018; Sallet et al., 2013). Despite this progress, we still lack fundamental neuroanatomical details of the functional maps and parcellations within PFC 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 non-human hominoid brains contain neuroanatomical structures that other primate brains lack. For instance, the expanded 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 (Armstrong, Schleicher, Heyder, Maria, & Zilles, 1995; Petrides, 2019; Sanides, 1962; Welker, 1990).

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 non-human hominoids. Specifically, we cannot map non-human hominoid brains in the way that we can map the human brain due to ethical reasons. As such, examining the relationship between tertiary sulci and different types of functional and neuroanatomical maps across spatial scales is a unique opportunity specific to the human brain. In this paper, we propose that tertiary sulci in the human cerebral cortex serve as a coordinate map for linking neuroanatomical and functional properties of the human brain across spatial scales and modalities. Consideration of tertiary sulci as anatomical features allows the “cognitive globe” of PFC function to be mapped within individuals without relying on an average cortical surface or template across individuals within which tertiary sulci disappear (**Fig. 1**). 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.

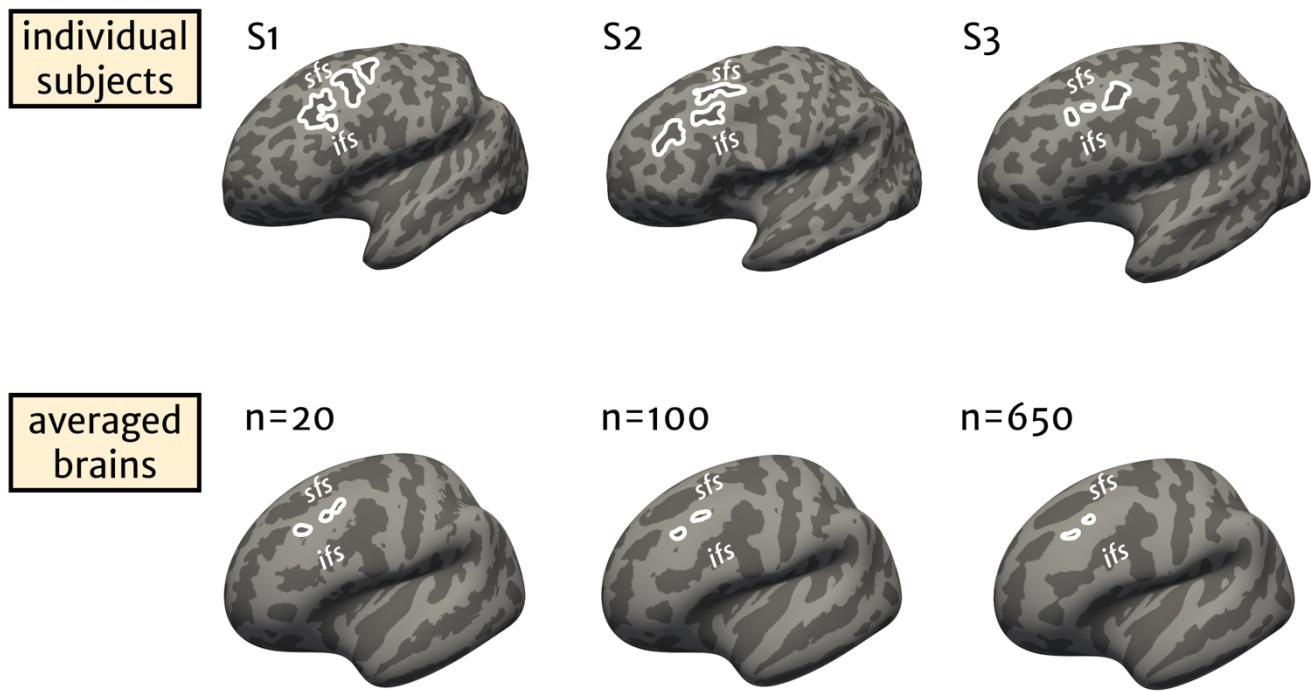
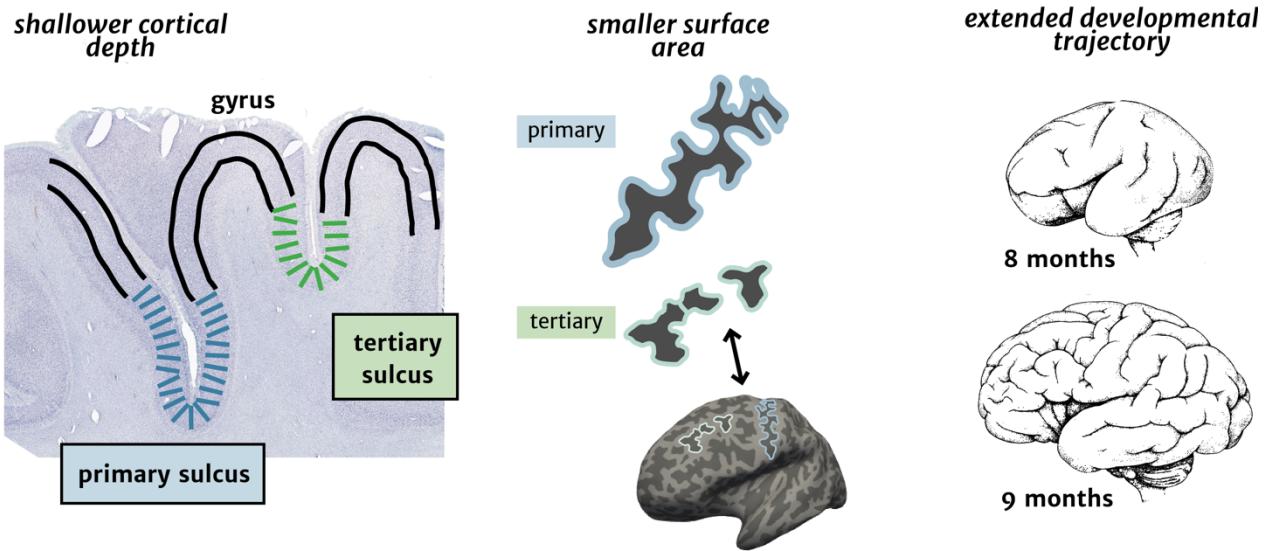


Figure 1. Tertiary sulci in LPFC disappear on averaged cortical surface reconstructions from anatomical MRIs. Top, three individually labeled left hemispheres with tertiary sulci in the middle frontal gyrus (MFG) outlined in white. The superior and inferior frontal sulci (*sfs*, *ifs*) are labeled for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

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.

a Principle characteristics of tertiary sulci



b Historical ambiguity over labeling tertiary sulci in MFG

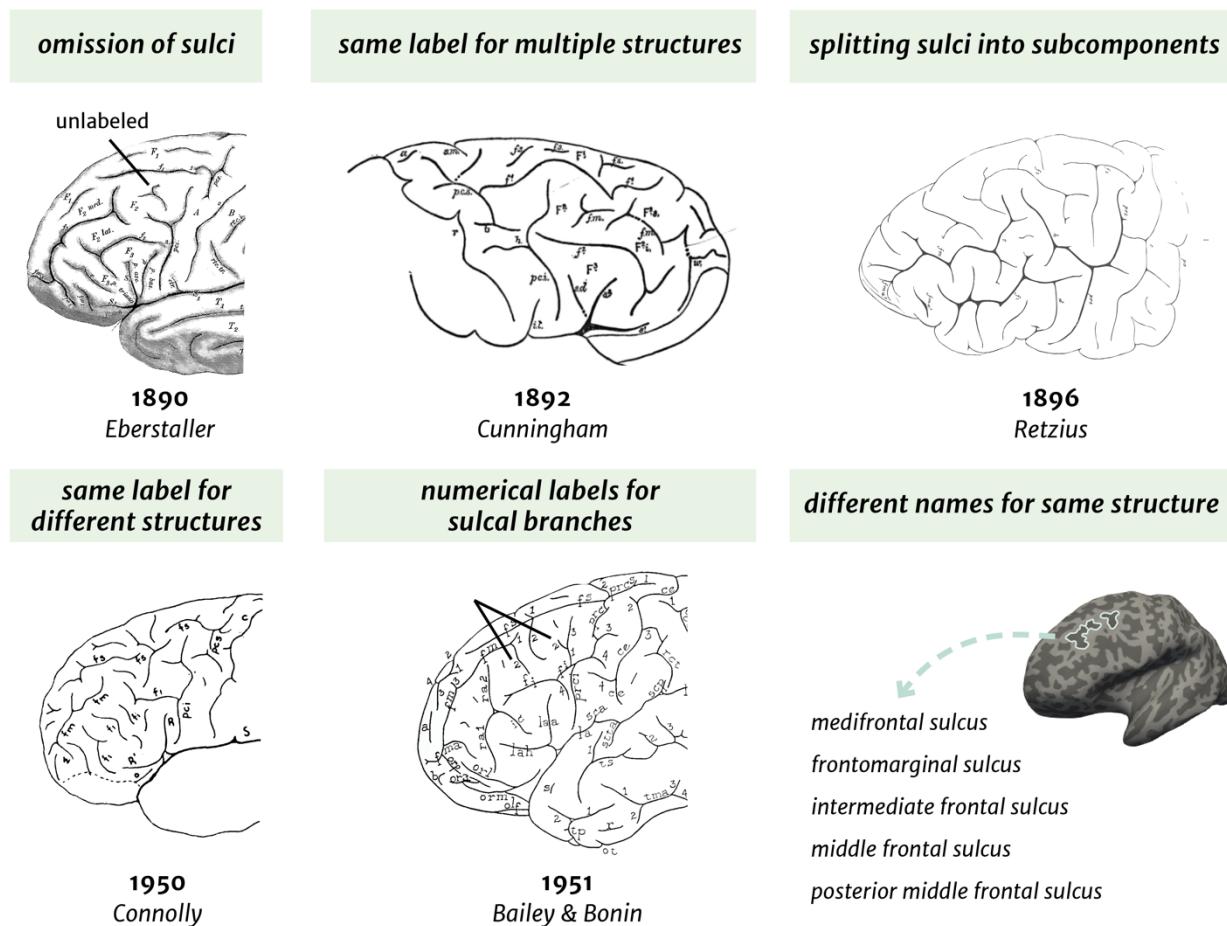


Figure 2. Characteristics of tertiary sulci in PFC and their historical identification. (a) Principle morphological features distinguishing tertiary sulci from larger primary sulci. Nissl stain downloaded from Allen atlas (<http://human.brain-map.org/>), developmental images adapted from Welker (1990). (b) We use the tertiary sulci in the posterior *middle frontal gyrus* (MFG) as an example to outline the main types of ambiguity across post-mortem studies leading to the neglect of tertiary sulci in LPFC. Top left, sulci in the MFG were depicted in diagrams and in individual samples but left unlabeled in official schematics as in Eberstaller (1890). Bottom left, a sulcus in the anterior MFG, the *frontomarginal sulcus*, was improperly used as the label for tertiary sulci in the more posterior MFG, as in Connolly (1950). Top middle, Cunningham (1892) used the same label of the *frontomarginal sulcus* for all tertiary sulci in the posterior MFG. Bottom middle, tertiary sulci were identified and even assigned numbers, but not given any distinguishing labels in brain sections or schematics (Connolly, 1950). Top right, separate labels were applied to different tertiary sulci within the posterior MFG. Retzius (1896) acknowledged a posterior transverse component (Retzius' *fmt* in Fig. 1) that was often distinct from the rest of the middle frontal sulcus. Ariens-Kappers (1928, 1929, 1936) also acknowledged three components of the middle frontal sulcus (Appendix) largely consistent with the most modern and thorough schematic of sulcal morphology from Petrides, which identifies the *posterior middle frontal sulcus* (*pmfs*) into three purported structures, an *anterior*, *intermediate*, and *posterior* component (Petrides, 2019). Bottom right, sulci within the MFG have been referred to using different labels (top, middle) such as the *medifrontal sulcus*, *frontomarginal sulcus*, *intermediate frontal sulcus*, *middle frontal sulcus*, and *posterior middle frontal sulcus*, among others (see Appendix).

I: LPFC tertiary sulci in classic anatomy and modern neuroimaging: Clarity vs. Ambiguity

It is widely accepted that LPFC has expanded with evolution (Amiez, Kostopoulos, Champod, & Petrides, 2006; Amiez & Petrides, 2009; Croxson et al., 2005; Neubert, Mars, Sallet, & Rushworth, 2015; Petrides, 2005; Petrides & Pandya, 1999; Petrides, Tomaiuolo, Yeterian, & Pandya, 2012; Sallet et al., 2013) and is “phylogenetically novel” (Stuss & Benson, 1984). This evolutionary expansion included the addition of anatomical structures within LPFC - such as tertiary sulci (Armstrong et al., 1995; Welker, 1990) - that are lacking in brains that are phylogenetically older (Barrett et al., 2020; Catani, 2019). Tertiary sulci are shallow indentations in the cerebral cortex that emerge latest in development (Fig. 2a). Ongoing research attempts to better understand the function of these evolved structures that are expanded, and even unique, to the human LPFC. Specifically, large, freely available multi-modal 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 post-mortem 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 post-mortem 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 and Pandya, 2012; Petrides, 2019), whereby tertiary sulci in LPFC were often undefined in classic atlases or contained different combinations of sulcal-label mappings (**Fig. 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 subjects 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 can be distinguished from veins and arteries in these reconstructions as they are in postmortem tissue. In terms of ambiguity, many researchers today analyze MRI data on cortical surfaces averaged across individuals (e.g. *fsaverage*, *MNI152*, and *Colin27* 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 (J. A. Miller, Voorhies, Lurie, D'Esposito, & Weiner, 2020), it may shrink or disappear when cortical surfaces are averaged together because LPFC tertiary sulci are more variable in location and much smaller compared to primary and secondary sulci (**Fig. 1**). The *posterior middle frontal sulcus*, a tertiary sulcus in LPFC discussed throughout this review, is about five times smaller (in terms of surface

area) and half as deep as the primary central sulcus. 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.

II: Developmental trajectory of LPFC tertiary sulci

Despite these historical and modern issues contributing to our lack of understanding of tertiary sulci within LPFC (**Fig. 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 cortex (Chi, Dooling, & Gilles, 1977; Welker, 1990). Instead, they emerge at different timepoints depending on the lobe they are in and also their topological positioning within that lobe. For the MFG, classic anatomists agreed that the *fronto-marginal* and *middle frontal* sulcal components emerged from anterior to posterior (**Fig. 3a**; Appendix). Between 16-24 weeks, the most anterior fronto-marginal components appear (Cunningham, 1892; Retzius, 1896; Turner, 1948), while 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 pre-term infants using MRI shows feasibility of this comparison. As illustrated in **Fig. 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* (**Fig. 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 (D. J. 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.

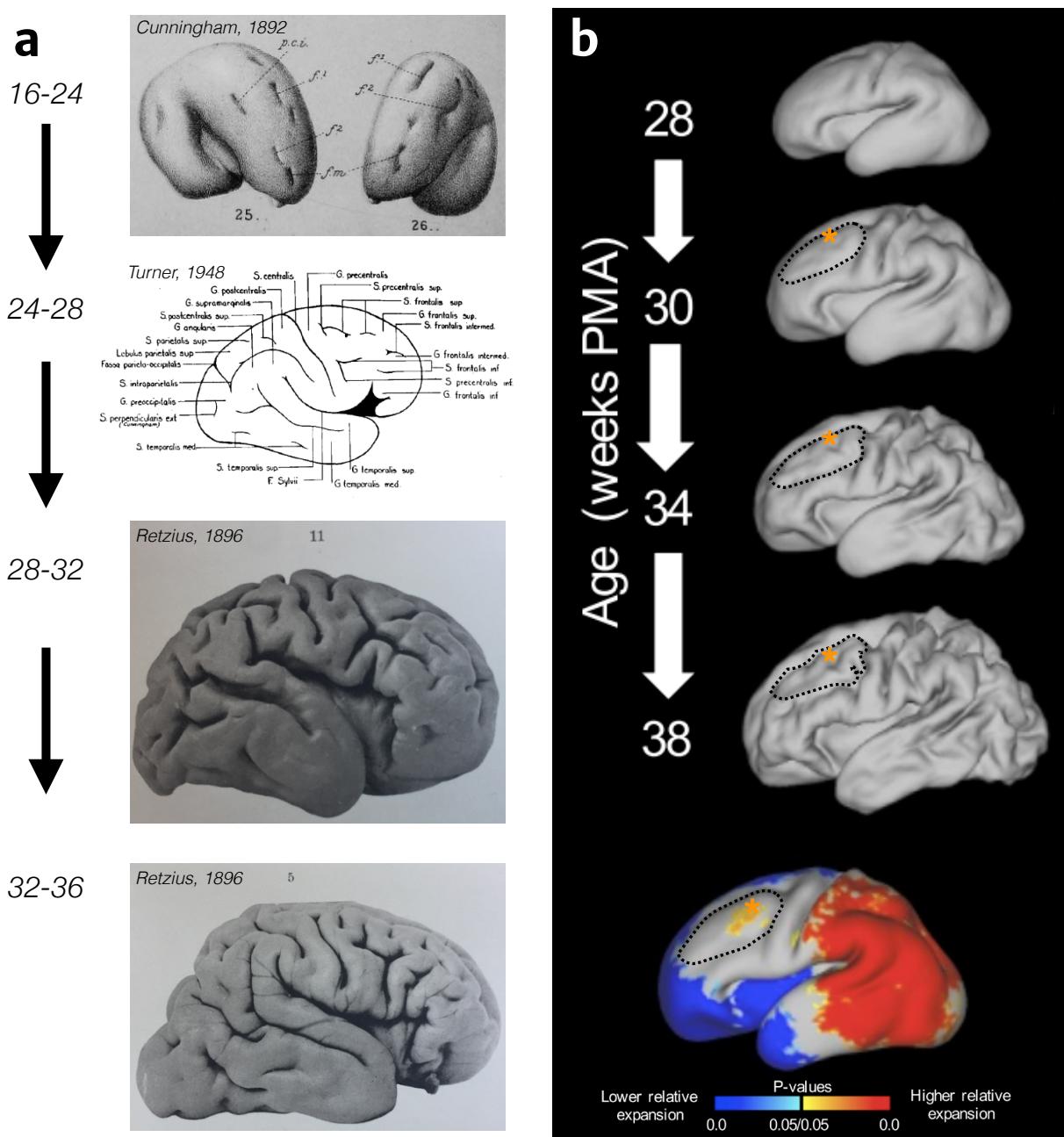


Figure 3. Sulci within the MFG likely emerge and develop along an anterior-posterior axis. **(a)** Top to bottom: Images from classic atlases and papers depicting the emergence of sulci during 16-24 weeks (Cunningham, 1892), 24-28 weeks (Turner, 1948), 28-32 weeks (Retzius, 1896), and 32-36 weeks (Retzius, 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, while 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 pre-term 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 7th and 8th month in gestation. Black lines outline the MFG, and asterisks show correspondence with the location of the posterior *pmfs* component (*pmfs-p*). Bottom: An average cortical surface map comparing the relative expansion across development.

III. Tertiary sulci in comparative neuroanatomy and primate evolution

Among primates, the level of cortical folding (or gyration 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 vmPFC using anatomical MRI from human, chimpanzee, baboon, and macaque brains. Across 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 (**Fig. 4a**). For example, the *dorsomedial polar sulcus* (*dmps*) was identified as a hominoid-specific marker present in most human brains and ~50% of chimpanzee brains, while the *ventromedial polar sulcus* (*vmps*) was present in most individual human brains (64%), but entirely absent in chimpanzees and other primate brains. Interestingly, while the presence of major cytoarchitectonic areas is largely conserved across species in vmPFC, the most expanded areas (BA 9 and 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 **Fig. 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 since the *pmfs* appears to delineate borders or transitional zones for cytoarchitectonic areas in both humans and chimpanzees. For example, the seminal papers of Rajkowska & Goldman-Rakic analyzed the cytoarchitecture of the

LPFC within nine post-mortem human brains. In the presented coronal sections of cytoarchitectonic areas 9 and 46 (Fig. 4c), a common trend appears that the *posterior middle frontal sulcus* (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. Support for this hypothesis is evident from re-examining cytoarchitectonic studies of chimpanzees showing that the *pmfs* also appears to mark cytoarchitectonic transitions between granular regions FD and FD Δ in chimpanzee brains differing in the extent of granular cell proliferation in layer 3 (Bailey & Bonin, 1951; Bailey, Bonin, & McCulloch, 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 (Donahue et al., 2018; Garcia-Cabezas, Zikopoulos, & Barbas, 2019; Van Essen et al., 2019).

As tertiary sulci are identified as important landmarks in functional areas that are most expanded 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 non-human primates (Badre, Frank, & Moore, 2015), these anatomical-behavioral relationships can begin to shed light on PFC structural-functional relationships across evolutionary timescales.

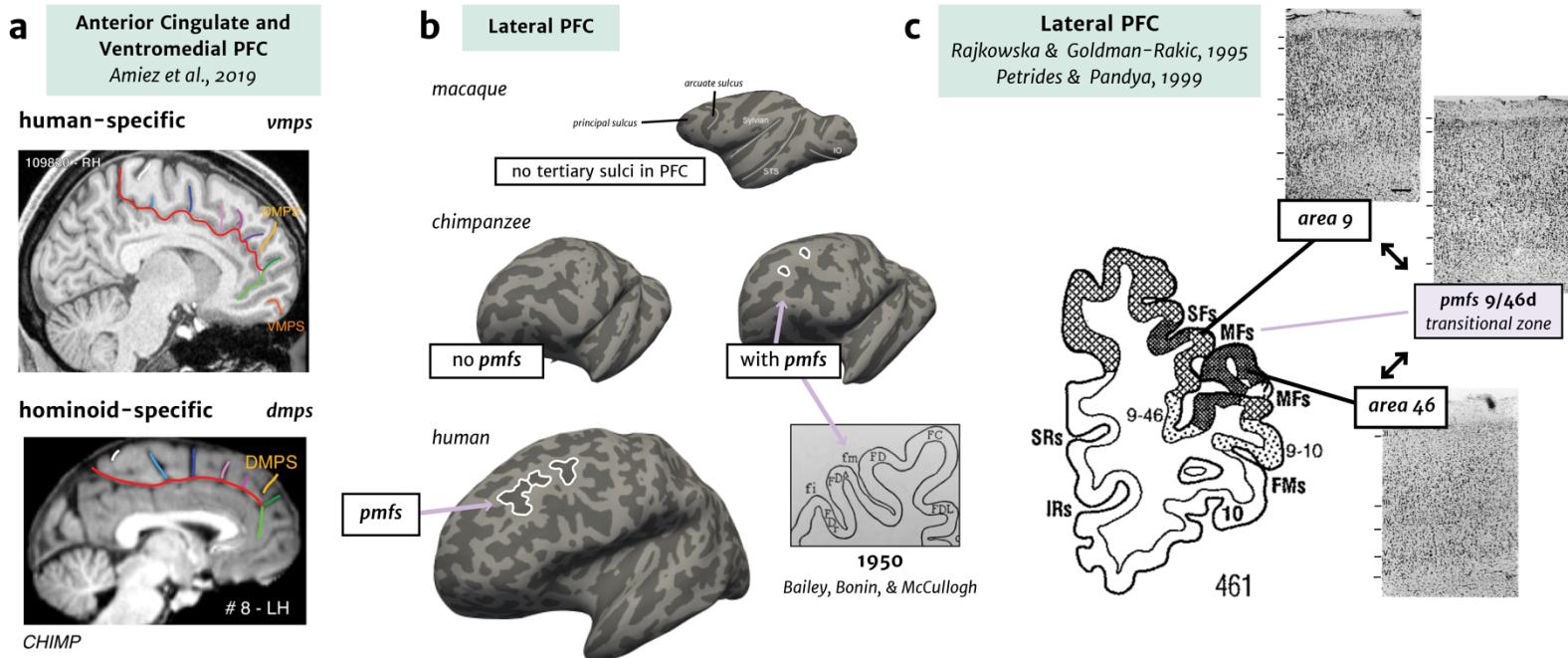


Figure 4. Tertiary sulci across primate PFC. (a) The sulcal morphology of the medial PFC and anterior cingulate cortex shown in example sagittal MRI sections of human and chimpanzee brains. The *vmps* (top) is a human-specific tertiary sulcus, while the *dmfs* (bottom) is found in humans and over half of 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>), where only the principal sulcus can be observed with the LPFC. Middle, two chimpanzee cortical surfaces showing variability in the presence or absence of a *pmfs* (outlined in white) within the MFG. The inset shows the *pmfs* (then labeled as “*fm*”) as the boundary between areas FD and FD Δ . Adapted from Bailey, Bonin, & McCulloch (1950). Bottom, example human cortical hemisphere with the prominent *pmfs* outlined in white. (c) Schematic of a post-mortem coronal section with the *pmfs* (labeled then as the *middle frontal sulcus*, *MFS*) indicating a transitional area between cytoarchitectonic areas 9 and 46. Insets show Nissl stains of cytoarchitectural organization in areas 9, 46, and transitional area 9/46d. Figures adapted from Rajkowska & Goldman-Rakic, 1995, and Petrides & Pandya, 1999.

IV: 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 in order to determine brain-behavioral relationships (Stuss, 2011; Stuss & Alexander, 2000; Stuss & Levine, 2002). 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, pg. 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 pgs. 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 multi-modal 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 ventral medial PFC (vmPFC) was carefully divided into four distinct patterns across individuals and the superior rostral sulcus (*ros-s*), a tertiary sulcus, was found to co-localize with a hub of the default mode network (Lopez-Persem, Verhagen, Amiez, Petrides, & Sallet, 2019). Further, 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 (**Fig. 5a**). Moreover, individual differences showed higher connectivity strength of the vmPFC with the rest of the default-mode network in individuals with a *ros-i* (64.04%) compared to those without a *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 PCC that was not present in individuals lacking a *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 from post-mortem brains (Petrides, 2019) to test whether these sulci could be defined in the LPFC of individual subjects *in-vivo*. Within each of 72 individual hemispheres, we identified the *pmfs* as a prominent tertiary sulcal structure that consists of three distinct components along an

anterior-posterior axis. While 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, as well as contributes to its disappearance in commonly used average cortical surfaces (Miller et al., 2020). To determine if *pmfs* components have distinct functional network organization, we analyzed multi-modal data from the Human Connectome Project (HCP) after manual labeling of all sulci in lateral PFC. 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 (**Fig. 5b**). Together, these results show that each *pmfs* component has a different network *fingerprint* (**Fig. 5b**).

The combination of these results with additional recent findings show the functional relevance of using tertiary sulci to study functional organization and properties (Amiez et al., 2006; Amiez et al., 2013; Amiez & Petrides, 2009; Lorenz et al., 2017; Weiner et al., 2014; Weiner et al., 2018). Because tertiary sulci are prominent within individuals, they can serve as a scaffolding to link microanatomical and functional features across all of the cerebral cortex and allow for communication and replication between research groups. 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 for 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.

Initial evidence for tertiary sulci as landmarks in human prefrontal cortex

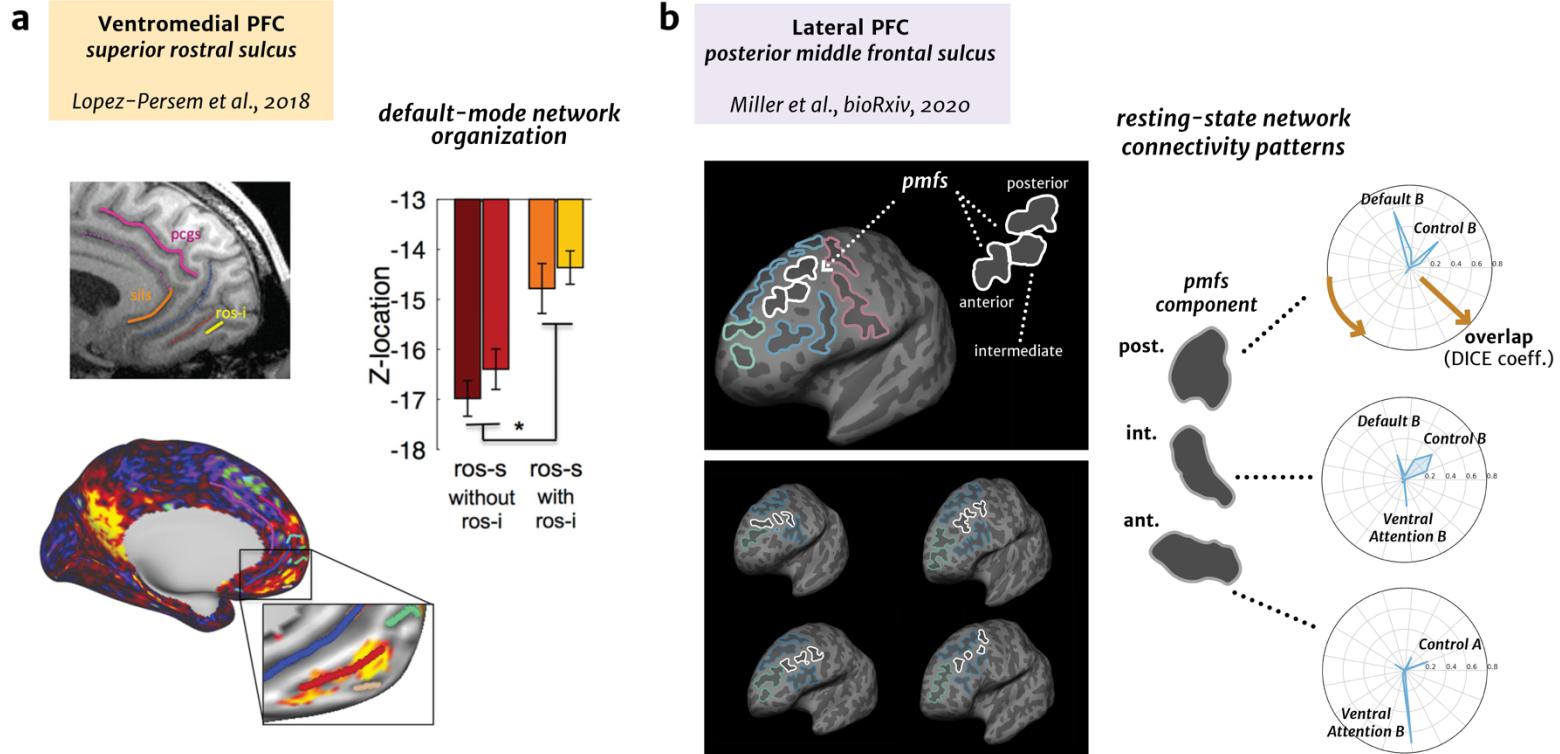


Figure 5. Network insights from identifying tertiary sulci. (a) The *superior* and *inferior rostral sulci* (*ros-s*, *ros-i*) serve as landmarks for default-mode network connectivity strength and organization. Top left, sulcal organization in vmPFC showing the inferior rostral tertiary sulcus (*ros-i*). Bottom Left, the location of peak 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 a *ros-i* show a shift in the peak location of default-mode network connectivity in the vmPFC. Figures adapted from Lopez-Persem et al. (2018). (b) Left, the three components of the *posterior middle frontal sulcus* (*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, adapted from Miller et al., 2020.

V: 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 & Vogt (1919) and further refined by Sanides (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 the Vogts, 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, 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 suggests that 1) the *pmfs-p* and *pmfs-i* likely identify boundaries between area *8Av* superiorly from *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* (Glasser et al., 2016). As this is a parcellation derived from averaging brain data across individuals, advancement in single-subject level parcellations that can be applied to new datasets will be needed to directly explore these hypotheses that tertiary sulci correspond to transitions between multimodal areas.

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 (**Fig. 6**, left). Functional and behavioral links are not limited to the location of *pmfs* components, but also other nearby tertiary sulci in LPFC. For instance, the intermediate frontal

sulcus (*imfs*), which is anterior to the *pmfs*, seems to identify a functional activations for the monitoring (or manipulation) of working memory content (Petrides, 2005); **Fig. 6**, right). Finally, a functional region preferentially activated during higher-order, temporal control appears to co-localize with the three *pmfs* components, while the *imfs* seems to co-localize with a functional region preferentially activated during contextual control (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 across different research groups and to ground functional maps to evolutionary new anatomical features of cortex. In sum, 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 species.

We emphasize that examining the relationship between tertiary sulci and other types of data presently requires accurate, validated, and manually defined sulci in individual subjects. For example, in our work, we manually defined ~800 sulci in 72 hemispheres. While 72 is a large sample size compared to other labor-intensive anatomical studies in which 20 hemispheres was considered sufficient to encapsulate individual differences (Amunts & Zilles, 2015), over 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, while 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. Future work using deep learning algorithms and expanded training data may help to identify tertiary structures in novel brains without manual labeling or intervention (Hao et al., 2020). Uncovering structural-functional

relationships in PFC will be advanced by leveraging anatomical expertise to develop computational approaches to neuroanatomy. This work is especially important as individual-level data has been increasingly recognized as important for basic and clinical human research, where it is critical to understand within-subject native anatomy, function, and behavior (Fisher, Medaglia, & Jeronimus, 2018; Gordon et al., 2017; Seitzman et al., 2019).

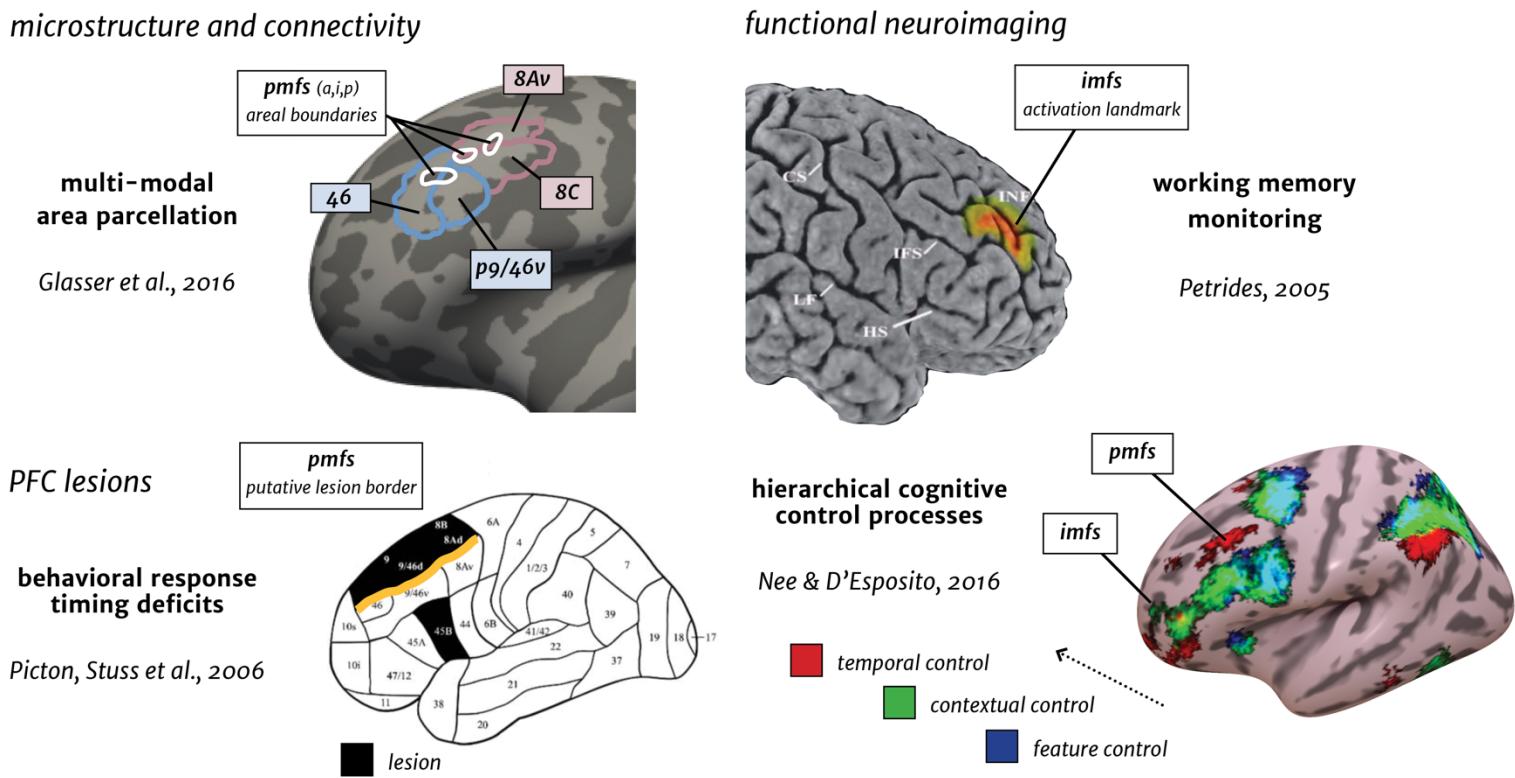


Figure 6. Tertiary sulci are useful for building an understanding of PFC across scales of organization. Tertiary sulci (*pmfs*, *imfs*) are relevant boundaries across studies of PFC organization, including multi-modal parcellations (Top left), lesions leading to response timing deficits (Bottom left), and functional neuroimaging of working memory and cognitive control (Right). Figures adapted from listed studies.

Open questions

- How many of the ~75 tertiary sulci in cortex serve as anatomical or functional 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?
- Can learning algorithms be developed to detect tertiary sulci within individual brains at a large-scale, given the limited ability for manual identification in large-n (1,000+) datasets?

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

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.

References

- Amiez, C., Kostopoulos, P., Champod, A. S., & Petrides, M. (2006). Local morphology predicts functional organization of the dorsal premotor region in the human brain. *J Neurosci*, 26(10), 2724-2731.
- Amiez, C., Neveu, R., Warrot, D., Petrides, M., Knoblauch, K., & Procyk, E. (2013). The location of feedback-related activity in the midcingulate cortex is predicted by local morphology. *J Neurosci*, 33(5), 2217-2228.
- Amiez, C., & Petrides, M. (2009). Anatomical organization of the eye fields in the human and non-human primate frontal cortex. *Prog Neurobiol*, 89(2), 220-230.
- Amiez, C., Sallet, J., Hopkins, W. D., Meguerditchian, A., Hadj-Bouziane, F., Ben Hamed, S., et al. (2019). Sulcal organization in the medial frontal cortex provides insights into primate brain evolution. *Nat Commun*, 10(1), 3437.
- Amunts, K., & Zilles, K. (2015). Architectonic Mapping of the Human Brain beyond Brodmann. *Neuron*, 88(6), 1086-1107.
- Armstrong, E., Schleicher, A., Heyder, O., Maria, C., & Zilles, K. (1995). The Ontogeny of Human Gyrification. *Cereb Cortex*, 5(1).
- Badre, D., & D'Esposito, M. (2009). Is the rostro-caudal axis of the frontal lobe hierarchical? *Nat Rev Neurosci*, 10(9), 659-669.
- Badre, D., Frank, M. J., & Moore, C. I. (2015). Interactionist Neuroscience. *Neuron*, 88(5), 855-860.
- Bailey, P., & Bonin, G. V. (1951). *The Isocortex of Man* (Vol. 1). Urbana: University of Illinois Press.
- Bailey, P., Bonin, G. V., & McCulloch, W. S. (1950). *The isocortex of the chimpanzee*. Urbana, IL: University of Illinois Press.
- Barrett, R. L. C., Dawson, M., Dyrby, T. B., Krug, K., Ptito, M., D'Arceuil, H., et al. (2020). Differences in Frontal Network Anatomy Across Primate Species. *J Neurosci*, 40(10), 2094-2107.
- Catani, M. (2019). The anatomy of the human frontal lobe. *Handb Clin Neurol*, 163, 95-122.
- Chi, J. G., Dooling, E. C., & Gilles, F. H. (1977). Gyral development of the human brain. *Ann Neurol*, 1(1), 86-93.
- Coalson, T. S., Van Essen, D. C., & Glasser, M. F. (2018). The impact of traditional neuroimaging methods on the spatial localization of cortical areas. *Proc Natl Acad Sci U S A*, 115(27), E6356-E6365.
- Crick, F., & Jones, E. (1993). Backwardness of human neuroanatomy. *Nature*, 361, 109-110.
- Croxson, P. L., Johansen-Berg, H., Behrens, T. E., Robson, M. D., Pinski, M. A., Gross, C. G., et al. (2005). Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J Neurosci*, 25(39), 8854-8866.
- Cunningham, D. J. (1892). *Contribution to the surface anatomy of the cerebral hemispheres*. Dublin: Academy House.
- Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*, 9(2), 179-194.
- Demirtas, M., Burt, J. B., Helmer, M., Ji, J. L., Adkinson, B. D., Glasser, M. F., et al. (2019). Hierarchical Heterogeneity across Human Cortex Shapes Large-Scale Neural Dynamics. *Neuron*, 101(6), 1181-1194 e1113.
- Donahue, C. J., Glasser, M. F., Preuss, T. M., Rilling, J. K., & Van Essen, D. C. (2018). Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates. *Proc Natl Acad Sci U S A*.
- Eickhoff, S. B., Yeo, B. T. T., & Genon, S. (2018). Imaging-based parcellations of the human brain. *Nat Rev Neurosci*, 19(11), 672-686.
- Ellis, C. T., & Turk-Browne, N. B. (2018). Infant fMRI: A Model System for Cognitive Neuroscience. *Trends Cogn Sci*, 22(5), 375-387.
- Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*, 9(2), 195-207.
- Fischl, B., Sereno, M. I., Tootell, R. B. H., & Dale, A. M. (1999). High-Resolution Intersubject Averaging and a Coordinate System for the Cortical Surface. *Human Brain Mapping*, 8, 272-284.

- Fisher, A. J., Medaglia, J. D., & Jeronimus, B. F. (2018). Lack of group-to-individual generalizability is a threat to human subjects research. *Proc Natl Acad Sci U S A*, 115(27), E6106-E6115.
- Garcia, K. E., Robinson, E. C., Alexopoulos, D., Dierker, D. L., Glasser, M. F., Coalson, T. S., et al. (2018). Dynamic patterns of cortical expansion during folding of the preterm human brain. *Proc Natl Acad Sci U S A*, 115(12), 3156-3161.
- Garcia-Cabezas, M. A., Zikopoulos, B., & Barbas, H. (2019). The Structural Model: a theory linking connections, plasticity, pathology, development and evolution of the cerebral cortex. *Brain Struct Funct*.
- Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., et al. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, 536(7615), 171-178.
- Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., et al. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage*, 80, 105-124.
- Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., et al. (2017). Precision Functional Mapping of Individual Human Brains. *Neuron*.
- Goulas, A., Uylings, H. B., & Stiers, P. (2012). Unravelling the intrinsic functional organization of the human lateral frontal cortex: a parcellation scheme based on resting state fMRI. *J Neurosci*, 32(30), 10238-10252.
- Hao, L., Bao, S., Tang, Y., Gao, R., Parvathaneni, P., Miller, J. A., et al. (2020). *Automatic Labeling of Cortical Sulci using Convolutional Neural Networks in a Developmental Cohort*. Paper presented at the IEEE International Symposium on Biomedical Imaging (ISBI)
- Henssen, A., Zilles, K., Palomero-Gallagher, N., Schleicher, A., Mohlberg, H., Gerboga, F., et al. (2016). Cytoarchitecture and probability maps of the human medial orbitofrontal cortex. *Cortex*, 75, 87-112.
- Koechlin, E., Ody, C., & Kouneiher, F. (2003). The Architecture of Cognitive Control in the Human Prefrontal Cortex. *Science*, 302.
- Koechlin, E., & Summerfield, C. (2007). An information theoretical approach to prefrontal executive function. *Trends Cogn Sci*, 11(6), 229-235.
- Kong, R., Li, J., Orban, C., Sabuncu, M. R., Liu, H., Schaefer, A., et al. (2018). Spatial Topography of Individual-Specific Cortical Networks Predicts Human Cognition, Personality, and Emotion. *Cereb Cortex*.
- Lopez-Persem, A., Verhagen, L., Amiez, C., Petrides, M., & Sallet, J. (2019). The Human Ventromedial Prefrontal Cortex: Sulcal Morphology and Its Influence on Functional Organization. *J Neurosci*, 39(19), 3627-3639.
- Lorenz, S., Weiner, K. S., Caspers, J., Mohlberg, H., Schleicher, A., Bludau, S., et al. (2017). Two New Cytoarchitectonic Areas on the Human Mid-Fusiform Gyrus. *Cereb Cortex*, 27(1), 373-385.
- Miller, D. J., Duka, T., Stimpson, C. D., Schapiro, S. J., Baze, W. B., McArthur, M. J., et al. (2012). Prolonged myelination in human neocortical evolution. *Proc Natl Acad Sci U S A*, 109(41), 16480-16485.
- Miller, E. K., & Cohen, J. D. (2001). AN INTEGRATIVE THEORY OF PREFRONTAL CORTEX FUNCTION. *Annu Rev Neurosci*, 24, 167-202.
- Miller, J. A., Voorhies, W., Lurie, D. J., D'Esposito, M., & Weiner, K. S. (2020). A new sulcal landmark for anatomical and functional gradients in human lateral prefrontal cortex *bioRxiv*
- Nee, D. E., & D'Esposito, M. (2016). The hierarchical organization of the lateral prefrontal cortex. *eLife*, 5.
- Neubert, F. X., Mars, R. B., Sallet, J., & Rushworth, M. F. (2015). Connectivity reveals relationship of brain areas for reward-guided learning and decision making in human and monkey frontal cortex. *Proc Natl Acad Sci U S A*, 112(20), E2695-2704.
- Petrides, M. (2005). Lateral prefrontal cortex: architectonic and functional organization. *Philos Trans R Soc Lond B Biol Sci*, 360(1456), 781-795.
- Petrides, M. (2019). *Atlas of the Morphology of the Human Cerebral Cortex on the Average MNI Brain* (1 ed.). London, UK: Elsevier.

- Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci*, 11, 1101-1036.
- Petrides, M., Tomaiuolo, F., Yeterian, E. H., & Pandya, D. N. (2012). The prefrontal cortex: comparative architectonic organization in the human and the macaque monkey brains. *Cortex*, 48(1), 46-57.
- Rajkowska, G., & Goldman-Rakic, P. S. (1995a). Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. *Cereb Cortex*, 5(4), 307-322.
- Rajkowska, G., & Goldman-Rakic, P. S. (1995b). Cytoarchitectonic Definition of Prefrontal areas in the Normal Human Cortex: II. Variability in Locations of Areas 9 and 46 and Relationship to the Talairach Coordinate System. *Cereb Cortex*, 5.
- Reid, A. T., Bzdok, D., Langner, R., Fox, P. T., Laird, A. R., Amunts, K., et al. (2016). Multimodal connectivity mapping of the human left anterior and posterior lateral prefrontal cortex. *Brain Struct Funct*, 221(5), 2589-2605.
- Retzius, G. (1896). *Das Menschenhirn*. Stockholm, Sweden: Norstedt and Soener.
- Reveley, C., Seth, A. K., Pierpaoli, C., Silva, A. C., Yu, D., Saunders, R. C., et al. (2015). Superficial white matter fiber systems impede detection of long-range cortical connections in diffusion MR tractography. *Proc Natl Acad Sci U S A*, 112(21), E2820-2828.
- Sallet, J., Mars, R. B., Noonan, M. P., Neubert, F. X., Jbabdi, S., O'Reilly, J. X., et al. (2013). The organization of dorsal frontal cortex in humans and macaques. *J Neurosci*, 33(30), 12255-12274.
- Sanides, F. (1962). Die Architektonik Des Menschlichen Stirnhirns Zugleich Eine Darstellung Der Prin. In M. Muller, H. Spatz & P. Vogel (Eds.), *Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie* (Vol. 98, pp. 176-190). Berlin: Springer Berlin Heidelberg.
- Sanides, F. (1964). STRUCTURE AND FUNCTION OF THE HUMAN FRONTAL LOBE. *Neuropsychologia*, 2, 209-219.
- Schilling, K., Gao, Y., Janve, V., Stepniewska, I., Landman, B. A., & Anderson, A. W. (2018). Confirmation of a gyral bias in diffusion MRI fiber tractography. *Hum Brain Mapp*, 39(3), 1449-1466.
- Seitzman, B. A., Gratton, C., Laumann, T. O., Gordon, E. M., Adeyemo, B., Dworetzky, A., et al. (2019). Trait-like variants in human functional brain networks. *Proc Natl Acad Sci U S A*, 116(45), 22851-22861.
- Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *J Int Neuropsychol Soc*, 17(5), 759-765.
- Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychol Res*, 63, 289-298.
- Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia*, 43(3), 396-417.
- Stuss, D. T., & Benson, D. F. (1984). Neuropsychological Studies of the Frontal Lobes. *Psychological Bulletin*, 95(1), 3-28.
- Stuss, D. T., & Knight, R. T. (2012). *Principles of Frontal Lobe Function* (2 ed.). Oxford: Oxford University Press.
- Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu Rev Psychol*, 53, 401-433.
- Turner, O. A. (1948). Growth and development of the cerebral cortical pattern in man. *Arch Neurol Psychiatry*, 59(1).
- Van Essen, D. C., Donahue, C. J., Coalson, T. S., Kennedy, H., Hayashi, T., & Glasser, M. F. (2019). Cerebral cortical folding, parcellation, and connectivity in humans, nonhuman primates, and mice. *Proc Natl Acad Sci U S A*.
- Van Essen, D. C., Jbabdi, S., Sotiroopoulos, S. N., Chen, C., Dikranian, K., Coalson, T. S., et al. (2014). Mapping Connections in Humans and Non-Human Primates. In *Diffusion MRI* (pp. 337-358).

- Weiner, K. S., Golarai, G., Caspers, J., Chuapoco, M. R., Mohlberg, H., Zilles, K., et al. (2014). The mid-fusiform sulcus: a landmark identifying both cytoarchitectonic and functional divisions of human ventral temporal cortex. *Neuroimage*, 84, 453-465.
- Weiner, K. S., Natu, V. S., & Grill-Spector, K. (2018). On object selectivity and the anatomy of the human fusiform gyrus. *Neuroimage*, 173, 604-609.
- Welker, W. (1990). Why does cerebral cortex fissure and fold? A review of determinants of gyri and sulci. In A. Peters & E. G. Jones (Eds.), (pp. 3-136). New York: Plenum Press.
- Zilles, K., Palomero-Gallagher, N., & Amunts, K. (2013). Development of cortical folding during evolution and ontogeny. *Trends Neurosci*, 36(5), 275-284.