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Nicholas Martin Singletary April 12, 2016

Parceling dorsal and medial frontal cortex in humans and chimpanzees with structural connectivity

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Abstract

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The dorsomedial prefrontal cortex is a region of cerebral cortex that shows functional activation during social cognitive tasks in humans and chimpanzees. However, the nature of the anatomical regions that support these functional activations is unknown, and this region's structural connections to other brain regions is debated. Therefore, we propose a new method for parceling cortex based on searching for borders of connectivity. Using this approach, we discovered three apparently homologous regions in humans and chimpanzees within the vicinity of dmPFC: dorsomedial rim, frontal pole, and cingulate cortex. The parcels that resulted from these borders conform to the borders of dmPFC as identified by functional activation studies and meta-analyses of brain regions involved in social cognition. These structural connectivity maps provide another means for noninvasive anatomical mapping of the cerebral cortex.

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Introduction

The default mode network is an interconnected set of cortical regions in humans that shows decreased activation during externally directed tasks and *increased* activation during rest, based on results from functional neuroimaging (Raichle et al. 2001) (Figure 1). These regions are hypothesized to be members of a network for social cognition, most notably for theory of mind, the ability to represent others' and one's own mental states (Buckner, Andrews-Hanna, and Schacter 2008). The default mode network is also associated with self-relevant processes, such as autobiographical memory (Andreasen et al. 1995) and simulating future events (Buckner and Carroll 2007). This network includes the lateral temporal cortex, posterior cinglulate/retrosplenial cortex, inferior parietal lobule, hippocampal formation, ventromedial prefrontal cortex (vmPFC), and the dorsomedial prefrontal cortex (Buckner, Andrews-Hanna, and Schacter 2008). Our study focuses on one of these regions known to exist in humans and chimpanzees, our closest extant evolutionary relatives: the functionally defined dorsomedial prefrontal cortex (dmPFC).

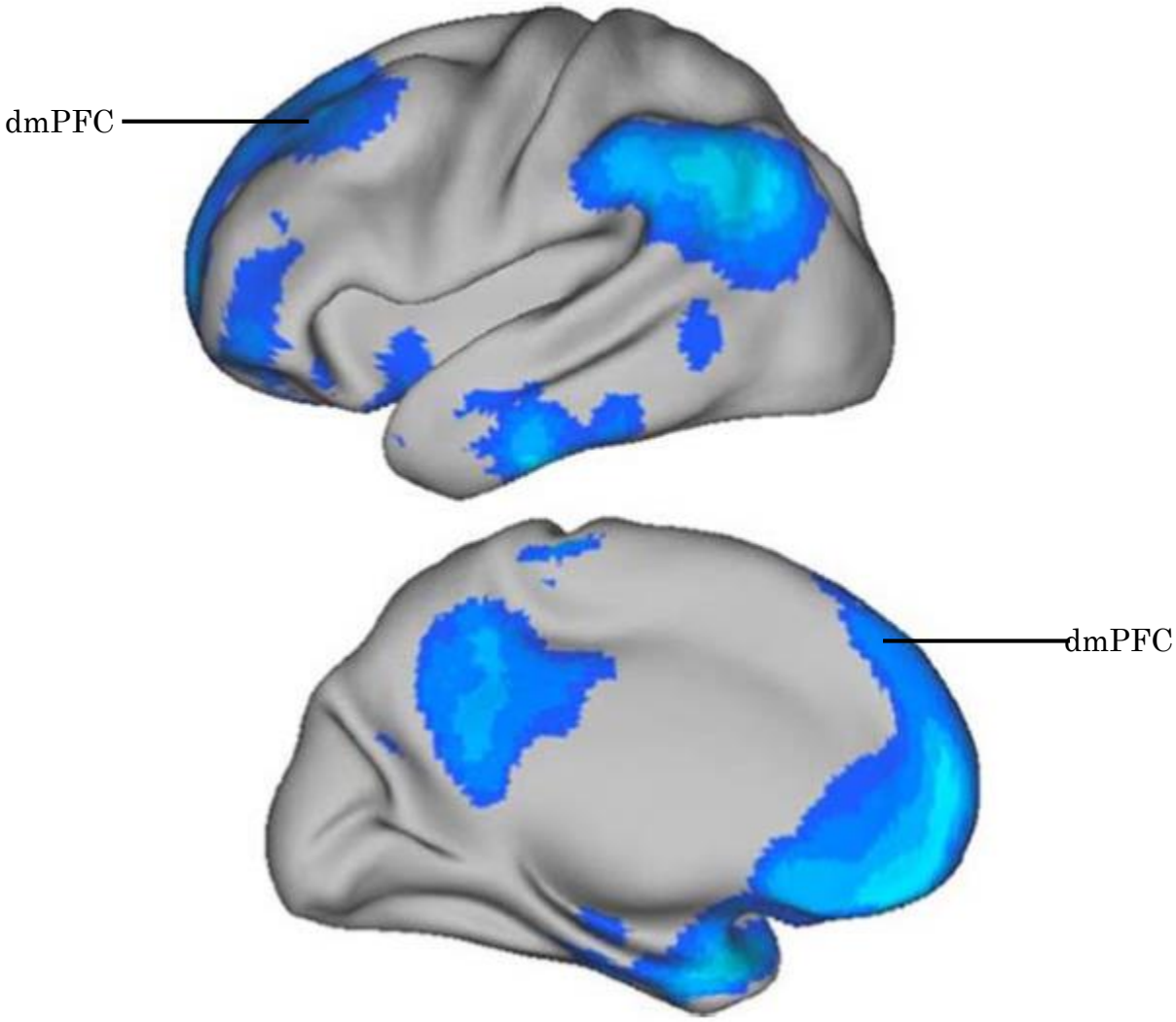


Figure 1. Visualization of the default mode network on the cortical surface according to resting-state positron emission tomography (PET), a form of functional neuroimaging. Data from Shulman et al. (1997), figure from Buckner, Andrew-Hanna, and Schacter (2008). Used with permission.

Functional neuroimaging studies suggest a role of human dmPFC in social cognitive tasks such as theory of mind (Goel et al. 1995; Ochsner et al. 2005). It is activated during tasks in which subjects infer others' mental states and preferences (Mitchell, Macrae, and Banaji 2006), possibly by matching external stimuli with remembered information (Bzdok et al. 2013). For instance, its activation has been

doubly dissociated from that of vmPFC in a theory of mind task in which participants were asked to predict the preferences of others with similar and dissimilar political orientations. Participants showed greater activation in vmPFC when considering their own preferences and preferences of others with similar political beliefs, while dmPFC showed greater activation when participants thought about the preferences of those with dissimilar political beliefs (Mitchell, Macrae, and Banaji 2006). A meta-analysis on perspective-taking also found a ventral-dorsal distinction in medial prefrontal cortex, showing greater associations of vmPFC with reward and dmPFC with perspective-taking (Bzdok et al. 2013). Yet neither part of medial prefrontal cortex is *selectively* activated by inferring others' mental states (Saxe and Kanwisher 2003; Mitchell, Banaji, and Macrae 2005). Neuropsychological evidence also suggests against a direct role of dmPFC in theory of mind: one patient with an extensive bilateral lesion to medial prefrontal cortex and six patients with medial frontal lobe epilepsy showed no impairment in theory of mind (Bird et al. 2004; Farrant et al. 2005).

Instead, dmPFC may show selective activation to situations that require attention to three agents: shared attention between individuals for another object, or "triadic attention" (Saxe 2006; Williams et al. 2005), which may be particularly important for supporting collaboration (Tomasello et al. 2005). The temporo-parietal junction (TPJ) may be the primary module for theory of mind in particular (Saxe and Kanwisher 2003). On the other hand, activation of dmPFC during theory of mind tasks may be modulated by tasks related to psychological descriptors in

general, regardless of whether inferring another's mental state is necessary to said task (Saxe 2006; Mitchell, Banaji, and Macrae 2005). This hypothesis is consistent with strong functional connectivity between dmPFC and TPJ (Andrews-Hanna et al. 2010; Bzdok et al. 2013).

Chimpanzees show similar default mode activation patterns to humans during functional neuroimaging studies, especially in medial prefrontal cortex, dorsolateral prefrontal cortex, rostrolateral prefrontal cortex, and medial parietal cortex, including precuneus (Rilling et al. 2007; Barks, Parr, and Rilling 2013). The anatomical and functional similarities between the default mode network of humans and chimpanzees suggest that the network supports similar psychological operations in humans and chimpanzees (Rilling et al. 2007). Nevertheless, humans have traits of social cognition that chimpanzees and other nonhuman primates seem to lack. For example, while chimpanzees appear to infer others' goals, intentions, perception, and knowledge, they do not appear to understand how these states arise (Povinelli and Eddy 1996). In essence, they do not understand that that others' knowledge stems from perceptual experience. They do not appear to understand false beliefs (Call and Tomasello 2008), most likely because they do not understand that the individual who held the false belief did not obtain the information required to form a true belief. They may be able to understand an individual's intentions, but they cannot engage in joint intention nor attention (triadic attention) with other individuals, which typical humans can do (Tomasello et al. 2005). Considering that dmPFC may support this human cognitive specialty,

yet dmPFC also exists as a functionally defined region in chimpanzees, there may be differences in the structure and connections of the dmPFC, or in the default mode network in general, that support differences in social cognition between these two species.

The dmPFC is undoubtedly involved in social cognition, but the identity of the other structures it is connected with, and how those structures are organized into networks, is still unclear. It has been implicated as a potential hub in a putative social brain network identified through a structural imaging study of healthy human adults that defined regions of interest using a meta-analysis of previous social cognitive neuroscience studies (Li et al., n.d.). This subnetwork contains vmPFC and precuneus in addition to dmPFC. Strong functional connectivity has been revealed between human dmPFC and amygdala, hippocampus, vmPFC, precuneus, and orbitofrontal cortex (Eickhoff et al. 2014). Yet strong functional connectivity was also found between dmPFC and inferior frontal gyrus, TPJ, and middle temporal gyrus (Bzdok et al. 2013). On the other hand, an investigation of functional connectivity using brain regions selected for their involvement in social cognition suggests that dmPFC is strongly connected to temporal pole, lateral temporal cortex, and TPJ (Andrews-Hanna et al. 2010). While some differences between structural and functional connectivity are to be expected, such conflict in findings between functional connectivity studies alone demonstrates that further study of this node's connectivity is warranted.

Dorsomedial prefrontal cortex is a functionally defined region, meaning that its borders are not based on anatomical measures, such as structural connectivity or cytoarchitecture, but instead on activations observed in functional neuroimaging studies (Figure 2). These activations might represent the activation of several different anatomical areas. Adjacent areas frequently show functional similarities. Since functional imaging studies identify activation peaks, or clusters of activated voxels, based on an arbitrary statistical threshold, the relationship of the functional activation to the underlying anatomy can be obscure. Compounding this, the design of the specific task used in the study as a proxy for the actual cognitive ability of interest can affect the location of activations.

As a result, some studies have attempted to parcel dmPFC into separate areas by functional connectivity. Eickhoff et al. (2014) divide dmPFC into four clusters across both hemispheres using *k*-means clustering, a general algorithm for dividing data into clusters in which each data point belongs to the cluster with the closest mean. For connectivity studies that use neuroimaging data, this usually means grouping together contiguous brain voxels (three-dimensional pixels) that share similar connectivity profiles and separating them from voxels that do not. Eickhoff et al. identified four clusters: caudal-right, rostroventral, rostrodorsal, and caudal-left. However, their dmPFC region of interest was defined as the convergence of functional activations from only two neuroimaging studies on social judgments. Additionally, this dmPFC region of interest is in the frontal pole, which

does not intersect well with reported dmPFC activations in other studies, including one study with four of the same authors (Figure 2).

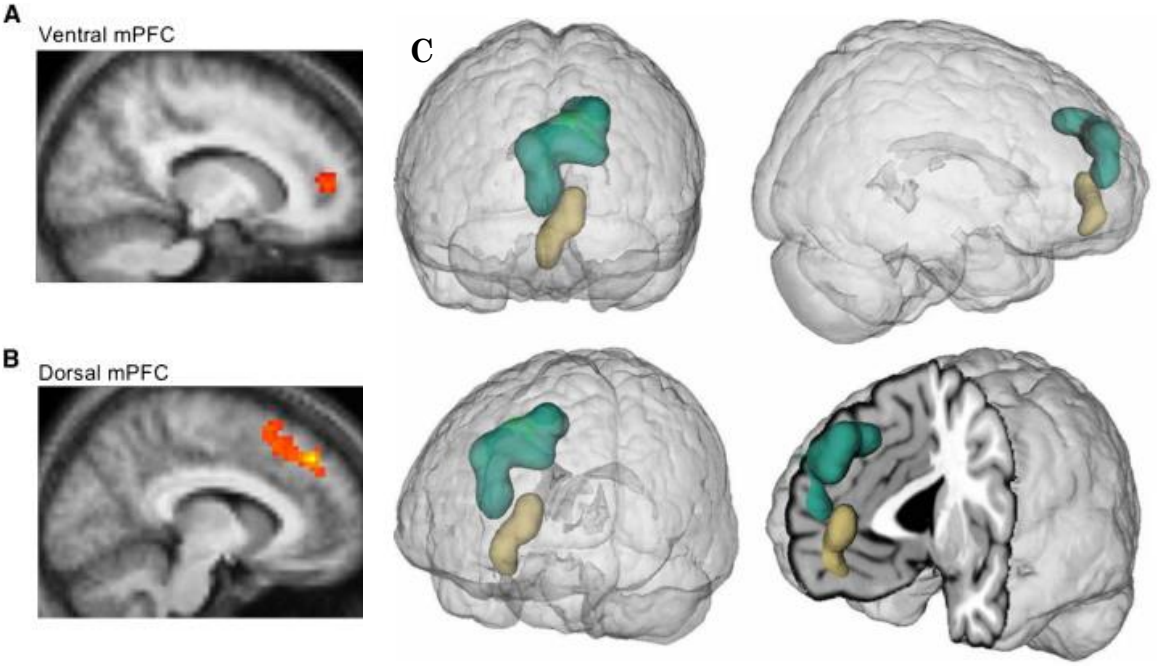


Figure 2. Functional neuroimaging reveals a double dissociation between vmPFC (A) and dmPFC (B) while study participants consider the preferences of persons with similar and dissimilar beliefs. A meta-analysis of functional neuroimaging studies related to perspective taking reveals similar results. Despite their anatomical names, the highlighted regions are **task-related** functional activations. This figure also demonstrates the ambiguity in naming regions which show task-related functional activations. These "anatomical" names are not always entirely anatomical. For instance, the region labeled vmPFC (A) actually appears to be in anterior cingulate cortex. When referring to the dmPFC, or any other functionally-defined region, are we referring to "a" standardized dmPFC that shows activity during many tasks, or are we referring an activation that was the result of one study that occurred in the dorsal part of the prefrontal cortex? A and B: Mitchell et al. (2006). C: Dorsomedial prefrontal cortex (green) and ventromedial prefrontal cortex (tan) as defined by Bzdok et al. (2013). A and B used with permission. C used in accordance with Creative Commons License.

Yet Sallet et al. (2013) and Neubert et al. (2014) parcel dorsal frontal cortex (DFC) by performing *k*-means clustering on data from diffusion-weighted imaging, which can reveal *structural* connectivity, the connectivity based on physical fiber tracts in the brain. Their DFC region of interest is fairly broad and indisputably contains regions that have been labeled dmPFC in previous studies. They then

measured the functional connectivity of these parcels to each other and to the rest of the brain. Finally, they compared results in humans to results in macaques. Despite major differences in social cognitive abilities, such as the presence of theory of mind in humans and its apparent absence in macaques, they found parcels of similar functional connectivity in macaques for every corresponding parcel in humans. In other words, they did not manage to find "new" regions in humans.

These studies raise three questions. Is dmPFC a "real," physical region consistently supported by similar anatomical regions across humans? If so, can we identify homologous anatomical regions in chimpanzees? If so, what are the anatomical regions that support functional activations in dmPFC? As a result of these open questions, for semantic purposes, we will take dmPFC to mean "dorsal and medial frontal cortex" for the remainder of this paper.

We cannot obtain new functional connectivity data from chimpanzees, our comparative species of interest, because of the recent decision at the National Institutes of Health to retire research on great apes, including noninvasive imaging research. However, our laboratory has available structural connectivity data obtained via diffusion tensor imagining (DTI), an imaging technique that uses properties of water diffusion to track fiber tracts in the brain. This approach uses data on structural connectivity in lieu of functional connectivity. Performing a structural connectivity study will also allow us to see if these task-dependent functional activations coincide with anatomical regions parceled by differences in structural connections.

In response to the rise of "big data" in connectomics, *k*-means clustering has become a common method for parceling cortex. Studies that employ *k*-means frequently delineate a target ROI, and then draw multiple circular "seed" ROIs centered on regions known to be connected to the target. This approach has been preferred by many researchers because they require fewer assumptions about the location of brain regions. This is particularly useful for the study of the connectivity of species whose neuroanatomy is not well known (Mars et al. 2014).

On the other hand, *k*-means clustering comes with its own set of assumptions. The most problematic assumption for neuroanatomy is the algorithm assumes that brain areas are discrete clusters that are highly stereotyped across individuals: contiguous with abrupt borders, without transition zones between areas, in all individuals. This is a useful approximation for primary sensory cortex, which has clear borders between areas and is stereotyped between individuals despite differences in developmental history. In contrast, the borders in association cortex (areas outside of primary sensory and motor areas), of which dmPFC is a part, are more ambiguous, and in some areas behave like gradients (Rosa and Tweedale 2005). Additionally, there might be more variation between the borders of regions in association cortex than in primary cortex (Rosa and Tweedale 2005). Therefore, association cortex may not lend itself as well to rigid parcellation schemes, such as *k*-means, as primary cortex. Yet regions in association cortex still have "connectivity fingerprints," or identifiable patterns of connectivity (Passingham, Stephan, and Kötter 2002), despite their less demarcated nature. In

addition to structural and functional connectivity, imaging provides another source information on the location and borders of cortical areas: myeloarchitecture, which can be assessed using T1- and T2-weighted structural MRI (Glasser and Van Essen 2011). Myeloarchitectonic borders potentially offer additional evidence in support of connectivity borders where the two types of borders coincide.

Therefore, we propose a novel method that reveals the structural connectivity of dmPFC, allows us to parcel it into separate regions based on said connectivity, and allows us to better define its borders using diffusion tensor imaging. To begin, we drew a broad region of interest (ROI) around dmPFC, including the dmPFC anterior to the central sulcus and superior to the cingulate sulcus, extending to the frontal pole. Then we tracked from this ROI to its inverse (all cortex that is not inside the ROI) in order to find territories with the highest probability of connections to dmPFC. Finally, we tracked connections from the other cortical regions back to dmPFC to identify connectivity borders within dmPFC. The most reliable borders will be those indicated by multiple connections.

We compared these parcels to gray matter cortical myelin maps to determine if there were other anatomical features that coincided with our parcels. We will validate the results of the chimpanzee dmPFC boundaries by determining if the hotspots of dmPFC activity as determined in Rilling et al. (2007) and Barks et al. (2013) fall within the same region as our putative chimpanzee dmPFC through qualitative analysis. This “border-finding” approach is inspired by approaches to tracing which, until the advent of structural neuroimaging, was the primary

method of tracking connections in the brain. This approach allows us to avoid prior assumptions on the location and shape of cortical regions while also avoiding assumptions inherent in *k*-means clustering. Therefore, we will also be able to analyze the ambiguity of the regions' borders, which will be imperative in a region of association cortex such as dmPFC.

Our goal is multifold. We determined the structural connectivity of dmPFC by tracking to its inverse and by parceling dmPFC into subregions based on major borders of structural connectivity and myeloarchitecture. Next, we determined the borders between dmPFC and adjacent regions. Finally, we compared our results between humans and chimpanzees. Then we use our maps to explore resemblances and differences in connectivity between humans and chimpanzees in the regions connected to the dmPFC. In turn, these dmPFC maps can be used as guides to identify and delineate other regions of the default mode network. We can also rank borders by strength.

Comparative neuroscience gives us insights into why brains are organized the way they are. This approach can inform the localization of functional areas and the search for primitives of cognition. We expect to obtain a detailed map of chimpanzee dorsal and medial frontal cortex from our study that can be used to identify and delineate other regions of the default mode network. This comparative study will increase our understanding the differences between the connections that support primates' social abilities and may elucidate the mechanisms supporting human social cognitive specialties.

Methods

Subjects and scanning

Morphologic, myeloarchitectonic, and diffusion tensor imaging (DTI) data for humans were retrieved from anonymized Human Connectome Project (HCP) MRI data (Van Essen et al. 2012). Data from 10 female subjects were chosen from the HCP 440 subjects data release based on scan quality. This dataset was designed to reflect the behavioral, ethnic, and socioeconomic diversity of the general population in the United States while excluding individuals with a history of neurodevelopmental, neuropsychiatric, or neurologic diseases. All participants were between 22 and 35 years old. Participants were scanned using a modified Siemens 3T MRI scanner. See Sotiropoulos et al. (2013) for details on data acquisition from humans.

Morphologic, myeloarchitectonic, and DTI data for chimpanzees (*Pan troglodytes*) comes from Yerkes's MRI scan collections, which have been pre-processed through the HCP pipeline (Glasser et al. 2013). Data from 19 female subjects were chosen based on scan quality. Chimpanzees were scanned in a Siemens 3T Trio scanner. Chimpanzees had been anesthetized before scanning. All procedures involving animals were carried out using procedures approved by the Yerkes Institutional Animal Care and Use Committee. See Chen et al. (2013) for additional details about chimpanzee scanning procedures.

In this study, factors of time and effort constrained us to examine connections in one hemisphere and in only one sex (females). We chose to focus on the right

hemisphere because the right dmPFC is more frequently studied in social cognitive neuroscience studies (Semrud-Clikeman and Hynd 1990). We chose females because of the possible ramifications of this project and similar projects for studies of dementia, which tends to be more common in females.

Analysis

Software

All datasets were analyzed using the HCP Workbench View application (Marcus et al. 2011, http://www.humanconnectome.org/software/get-connectome-workbench.html) and with the Oxford Centre for Functional MRI of the Brain Software Library (Jenkinson et al. 2012), which is the standard toolkit for carrying out probabilistic tractography with diffusion-weighted imaging. HCP Workbench represents the cerebral cortex as a mesh of vertices corresponding to the interface between gray and white matter.

Tracking algorithm

We delineated regions between which to track by drawing ROIs using HCP Workbench View. Our algorithm sent streamlines from a "seed" mask (R1) in the cortex to a waypoint mask (R2) in the cortex overlaid by a stop mask at the pial surface of the cortex. We sent 5000 streamlines per vertex in R1 that represented the gray matter/white matter interface within the ROI. The probability p that a streamline from R1 makes it to any vertex in R2 is given by the formula below, where N is the number of streamlines successfully passing through a voxel and W is

the waytotal (the number of streamlines sent from a seed that successfully make it to a vertex in the waypoint mask).

$$p(R1 \rightarrow R2) = \frac{N}{W}$$

The final probability is the probability that a streamline passes from R1 to R2 or from R2 to R1 or both, which is given by

$$P([R1 \rightarrow R2] \vee [R2 \rightarrow R1]) = p(R1 \rightarrow R2) + p(R2 \rightarrow R1) - p([R1 \rightarrow R2] \wedge [R2 \rightarrow R1])$$

We added a distance correction by multiplying the waytotals by the mean distance from the seed ROI. Then the probability maps for each tract are binarized with a threshold of $P > 5\times10^{-5}$ unless otherwise stated. Tracking back to extended dmPFC from the secondary ROIs required tighter probability thresholds ($5\times10^{-4} < P < 2.5\times10^{-3}$) to yield similar ROIs because chimpanzee cortex is smaller and/or because the quality of the chimpanzee scans was lower. The binarized maps for all subjects of a given species were combined to generate heat maps representing the percentage of subjects that met the probability threshold. The heat maps were then thresholded to display only those vertices that met criterion in at least 80 percent of subjects.

Connectivity borders

To begin, we drew a broad region of interest (ROI) that encompassed territories that have been identified as dmPFC in published studies on humans, including (n.d.) (Figure 3). This ROI includes the dmPFC anterior to the central sulcus and superior to the cingulate sulcus, extending to the frontal pole, containing all of dmPFC as described in Li et al. (Li et al., n.d.) (Figure 3). We tracked

connections from this dmPFC ROI to all the cortex of the same hemisphere that lay outside the dmPFC ROI (henceforth called the "inverse dmPFC") to reveal regions with high probability of connections to the dmPFC. We drew new ROIs around each contiguous cluster of connections, which we called connectivity-based, secondary ROIs (Figure 3, Figure 4). We then drew an even broader ROI around our original dmPFC ROI, which we call "extended dmPFC." This ROI includes anterior cingulate cortex and all of neocortex anterior to the central sulcus, and dorsal to the middle frontal sulcus. Although the anterior temporal lobe (ATL) did not show up as a connectivity hotspot in humans when we tracked to inverse dmPFC, we added an ATL secondary ROI anyway because of evidence from Andrews-Hanna et al. (2010) and a pilot analysis that indicated high connectivity from the ventral part of extended dmPFC to this region.

Human and chimpanzee data were analyzed independently by different people, while consulting on methods and thresholds.

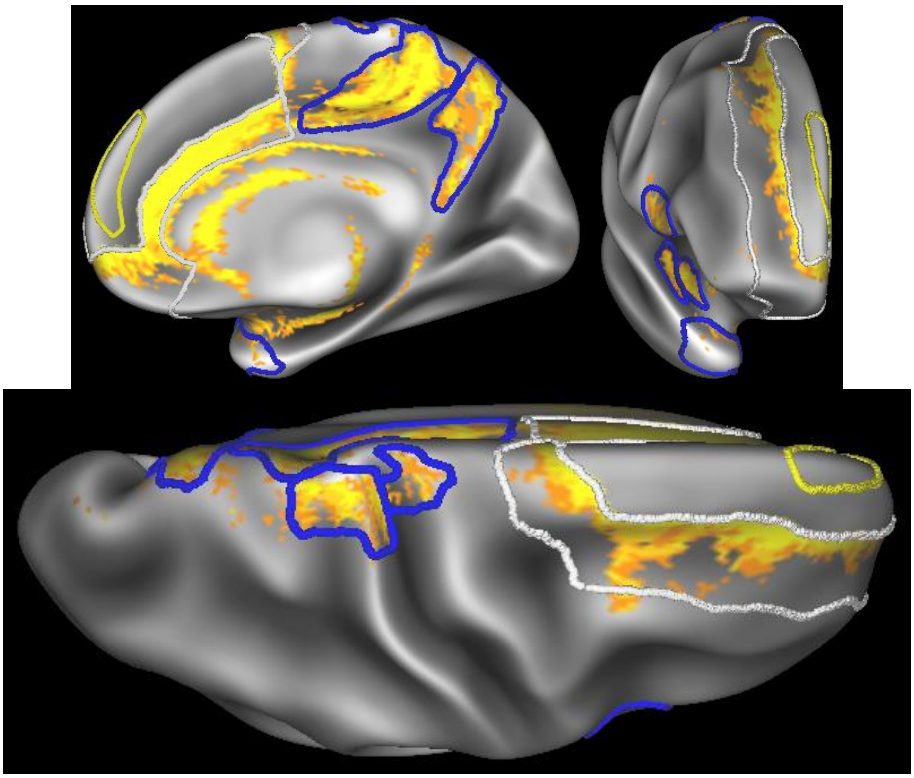


Figure 3. Dorsomedial prefrontal cortex and secondary ROIs. The dmPFC as described by Li et al (n.d.) is the yellow, innermost dmPFC ROI. This ROI is immediately encompassed by our dmPFC ROI in white. We tracked from this ROI to its inverse in order to obtain the yellow highlighted regions, which represent regions that show highly probable connections to our dmPFC. Extended dmPFC is the larger white outline. Contiguous regions that show probable connections to dmPFC are outlined with blue connectivity-based secondary ROIs.

In order to determine the location of connectivity borders within extended dmPFC, we displayed multiple combinations of connections within extended dmPFC, including connections of the secondary ROIs to dmPFC and the connections of the overlapping ROIs in extended dmPFC to their inverses. We drew candidate borders based on where multiple connections within extended dmPFC ended. This process was repeated in chimpanzees. This process divided extended dmPFC into "parcels," contiguous, closed regions that lie within borders.

We compared connectivity borders between humans and chimpanzees in a more detailed analysis in which we displayed the connections from five sets of secondary regions of interest that the two species had in common. One of the secondary ROIs, temporo-parietal junction, did not appear in humans during our initial search for secondary regions of interest, but we found it by decreasing the probability threshold to 5×10^{-6}. We drew new borders around the territories in extended dmPFC that showed connections to each of these five secondary ROIs and compared the results between humans and chimpanzees. Because TPJ and precuneus are two regions that are unambiguously part of the social brain network, we also paid close attention to the regions in both species where connections from those secondary ROIs overlap.

Myeloarchitectonic borders

In order to determine if other anatomical features coincided with our connectivity borders, we drew another set of borders to delineate the locations of rapid changes in the amount of cortical myelin based on the myelin gradient map provided in the HCP Workbench (Glasser and Van Essen 2011). We compare these myeloarchitectonic borders to the borders we drew based on the DTI connectivity data.

Comparison to known functional regions

We compared our dmPFC parcels to functional regions within the vicinity of dmPFC in humans and chimpanzees based on findings in Li et al. (n.d.).

A note on the figures: Most of the figures of human and chimpanzee cortex in this paper were created using Human Connectome Project Workbench. They display an inflated view of a cortex averaged across 440 individuals. The inflated view allows better visualization of areas that lie within sulci, which appear shadowed, while still maintaining the general shape of the cerebral cortex for easy recognition of anatomical regions.

Results

Identification of connectivity-based secondary ROIs

In humans, tracking to inverse dmPFC revealed highly probable connections to the following regions: anterior precuneus (APr), posterior precuneus (PPr), dorsal motor cortex (DM), dorsal parietal cortex (DPa), ventral premotor cortex (VPM), temporal operculum (TO), and ventral insula (VI) (Figure 4). Meanwhile, in chimpanzees, tracking to inverse dmPFC at the same probability threshold revealed highly probable connections to the cingulate sulcus (CgS), precuneus (Pr), dorsal central sulcus (DCS), VPM, VI, superior parietal lobule (SPL), temporo-parietal junction (TPJ), superior temporal sulcus (STS), and fronto-orbital sulcus (FOS) (Figure 5). Figure 5 also denotes possible homologs between secondary ROIs in humans and chimpanzees.

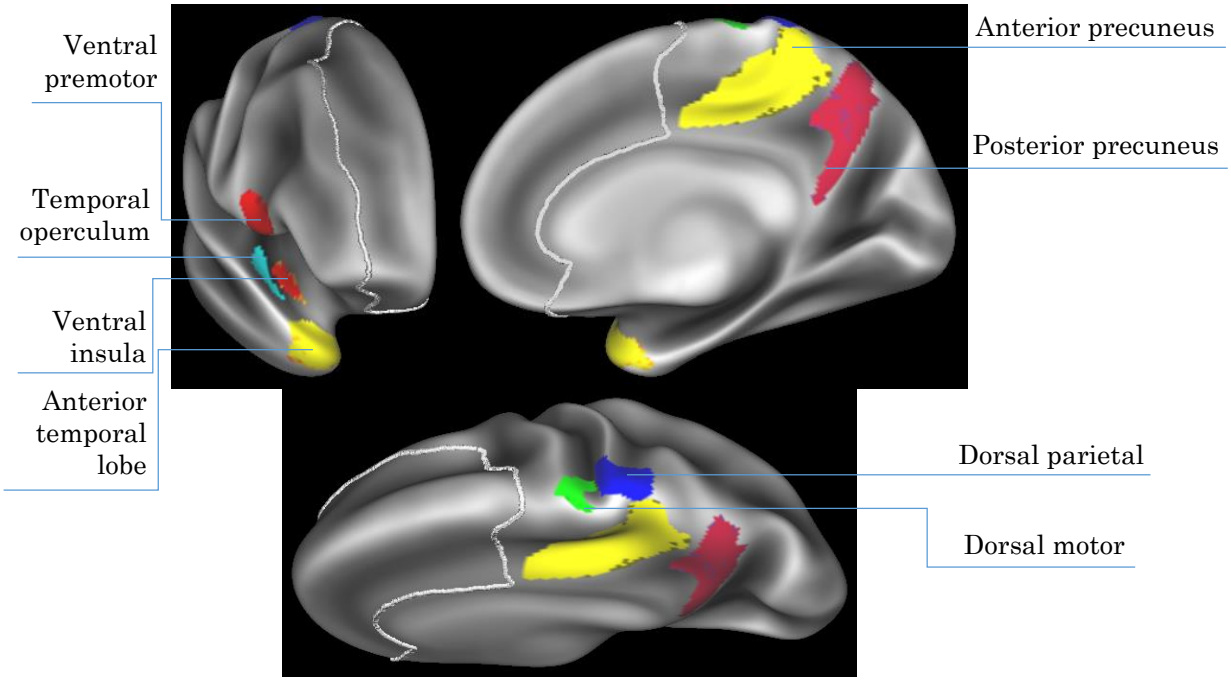


Figure 4. Secondary ROIs projected on the cortical surface derived from hotspots of connections from the inverse of dmPFC in humans.

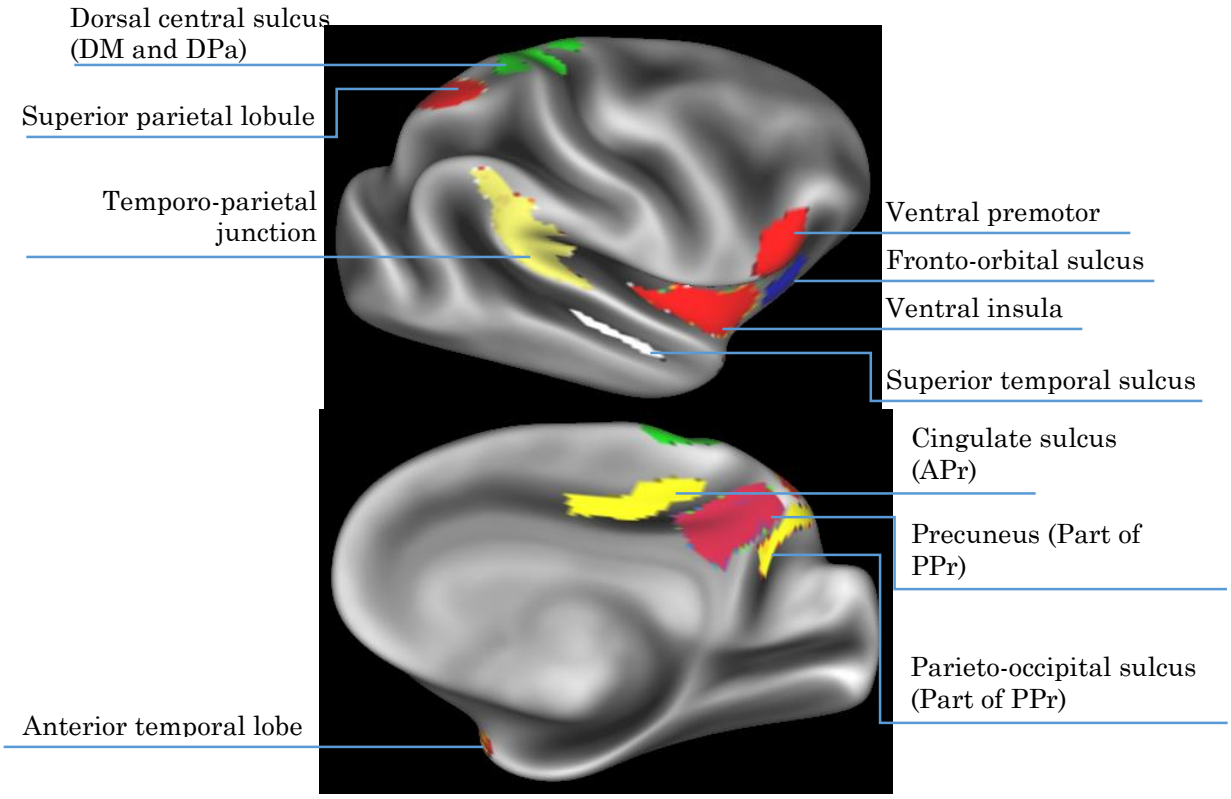


Figure 5. Secondary ROIs projected on the cortical surface derived from hotspots of connections from the inverse of dmPFC in chimpanzees. Names of likely human homologs are in parentheses.

Identifying connectivity borders

We identified 25 candidate borders in humans (Figure 6) and 21 candidate borders in chimpanzees (Figure 7). Table 1 and

Table 2 show which secondary ROIs support each border in humans and chimpanzees, respectively.

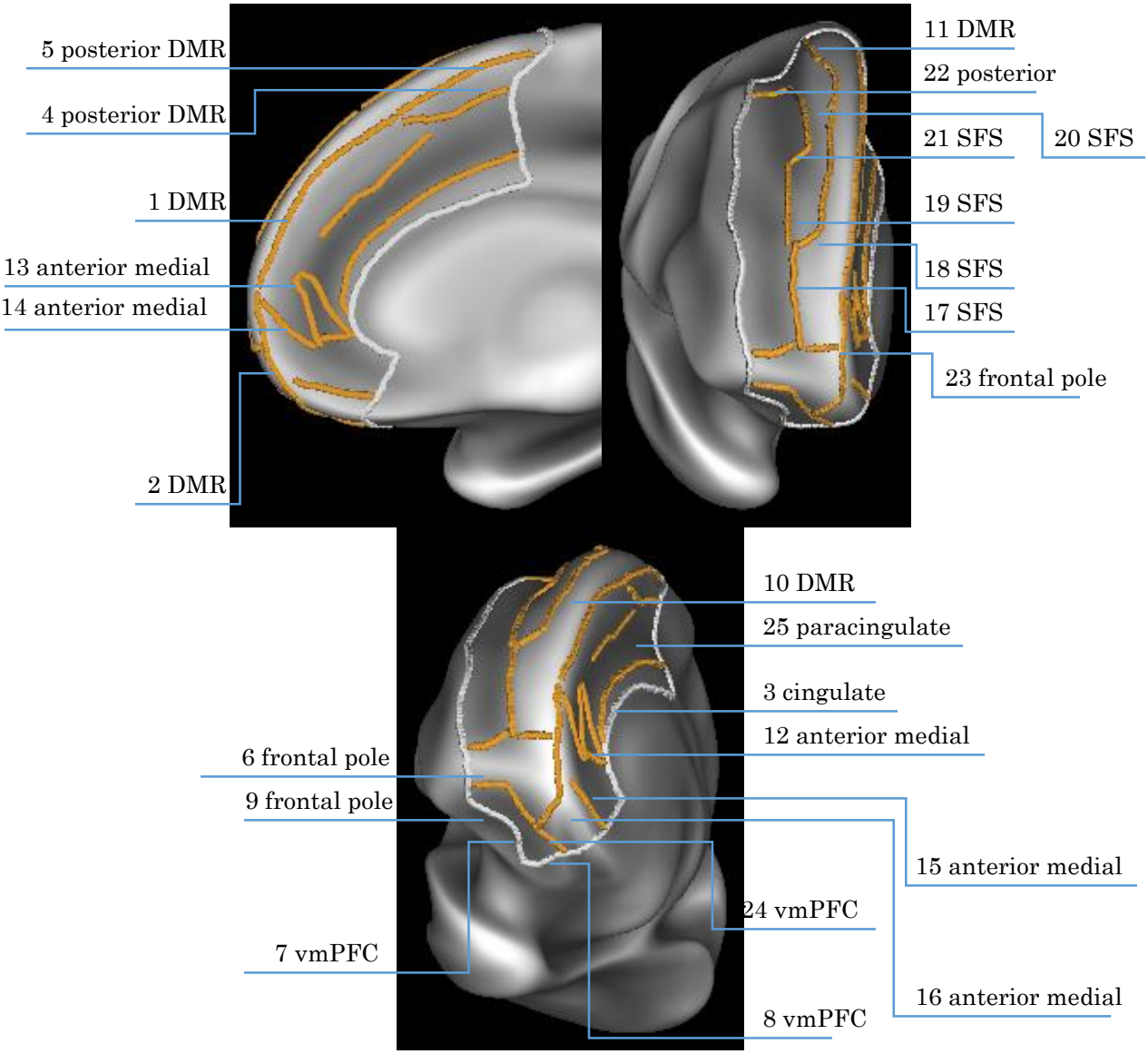


Figure 6. Candidate borders within human extended dmPFC identified from our connectivity analysis shown in orange. Extended dmPFC outlined in white. Abbreviations: DMR: Dorsomedial rim. SFS: superior frontal sulcus.

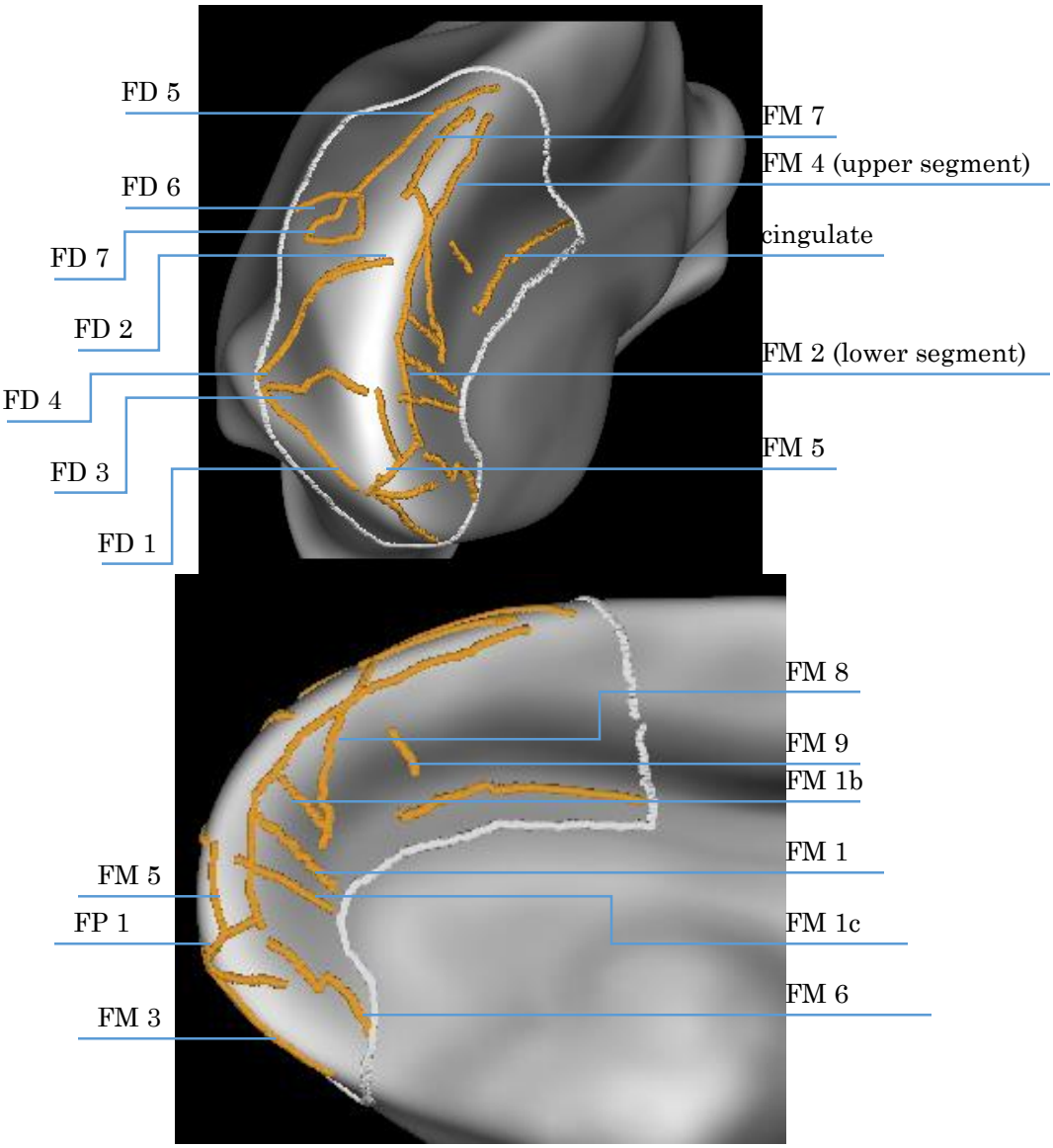


Figure 7. Candidate borders within chimpanzee extended dmPFC identified from our connectivity analysis shown in orange. Extended dmPFC outlined in white. Abbreviations: FM: frontal-medial. FD: frontal-dorsal. FP: frontal-polar.

Table 1. Connections from secondary ROIs that support each border in human extended dmPFC. VPM: Ventral premotor. DM: Dorsal motor. DP: Dorsal parietal. APr: Anterior precuneus. PPr: Posterior precuneus. TO: Temporal operculum. VI: Ventral insula. ATL: Anterior temporal lobe.

		Secondary ROIs							
		VPM (VPM)	DM (DCS)	DPa (DCS)	APr (CgS)	PPr (Pr)	TO (VI)	VI (VI)	ATL (ATL)
Borders	1 DMR	■	■	■			■	■	■
	2 DMR	■	■	■	■	■	■	■	■
	3 cingulate		■	■			■	■	■
	4 pDMR	■		■				■	
	5 pDMR		■				■		■
	6 FP		■	■		■	■	■	■
	7 vmPFC		■	■		■	■	■	■
	8 vmPFC								■
	9 FP		■	■		■	■	■	■
	10 DMR	■	■		■				
	11 DMR		■		■	■	■		■
	12 AM				■	■			
	13 AM				■	■			
	14 AM				■	■			
	15 AM								■
	16 AM								■
	17 SFS	■	■	■	■	■	■	■	■
	18 SFS					■	■		
	19 SFS	■	■	■			■	■	
	20 SFS	■		■				■	
	21 SFS		■	■				■	
	22 Posterior	■	■	■				■	
	23 FP	■			■				
	24 vmPFC		■	■		■	■	■	
	25 paracingulate			■					

Table 2. Connections from secondary ROIs that support each border in chimpanzee extended dmPFC. VPM: Ventral premotor. FOS: Fronto-orbital sulcus. VI: Ventral insula. ATL: Anterior temporal lobe. STS: Superior temporal sulcus. IPL: Inferior parietal lobule. DCS: Dorsal central sulcus. Pre: Precuneus. POS: Parieto-occipital sulcus. CgS: Cingulate sulcus.

		Secondary ROIs										
		VPM (VPM)	FOS	VI (VI, TO)	ATL (ATL)	STS	TPJ	SPL	DCS (DM, DP)	Pr (PPr)	POS (PPr)	CgS (APr)
Borders	FD1 (9 FP, 7 vmPFC, 8 vmPFC)		■	■	■	■	■	■	■		■	
	FD2			■			■	■	■		■	
	FD3		■		■	■						
	FD4							■			■	
	FD5 (19 SFS)	■							■			
	FM1						■			■		
	FM1b (AM ROIs?)									■		
	FM1c						■			■		
	FM2 (2 DMR)					■	■	■				
	FM3 (7 vmPFC, 8vmPFC?)				■	■						
	FM4 (1 DMR)	■					■	■	■	■		
	FM5		■	■								
	FM6			■		■					■	
	FP1		■	■			■		■			
	FD6	■					■		■			
	FM7			■			■	■		■	■	
	FD7	■		■			■	■	■			
	FM8											■
	FM9						■	■				■
	FD8			■								
	Cing. (3 Cing.)						■	■	■	■	■	■

Borders varied by the amount of evidence in support of them. "Strong borders" were the result of an edge where several overlapping connections abruptly stopped. "Weak borders" were the result of an edge where only one connection stopped. "Ambiguous borders" are supported by the edge of more than one overlapping connection, but these overlapping terminations were not located directly on top of one another. As examples of our border-finding process in humans,

we show support for the strong borders surrounding human dorsomedial rim (Figure 8) and cingulate gyrus (Figure 9), the weak border along the paracingulate sulcus (Figure 10), and the ambiguous border roughly perpendicular to the superior frontal sulcus (Figure 11). Table 3 contains an analysis of the strength of each candidate border in humans.

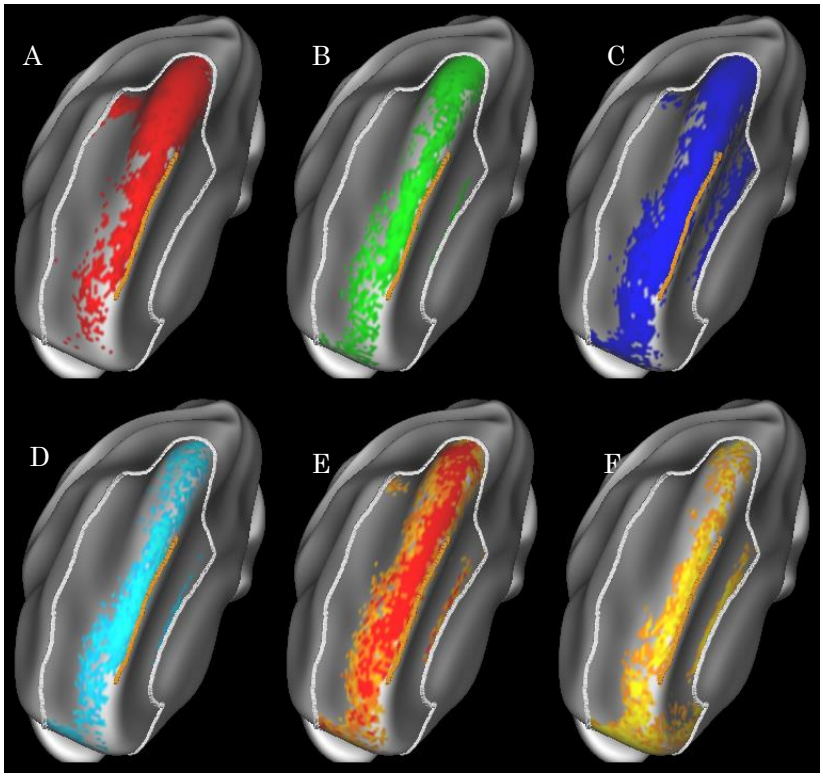


Figure 8. This "strong" border along the dorsomedial rim of human cerebral cortex (orange) is supported by connections from 6 secondary ROIs. A: From ventral premotor. B: Dorsal motor. C: Dorsal parietal. D: Temporal operculum. E. Ventral insula. F: Anterior temporal lobe.

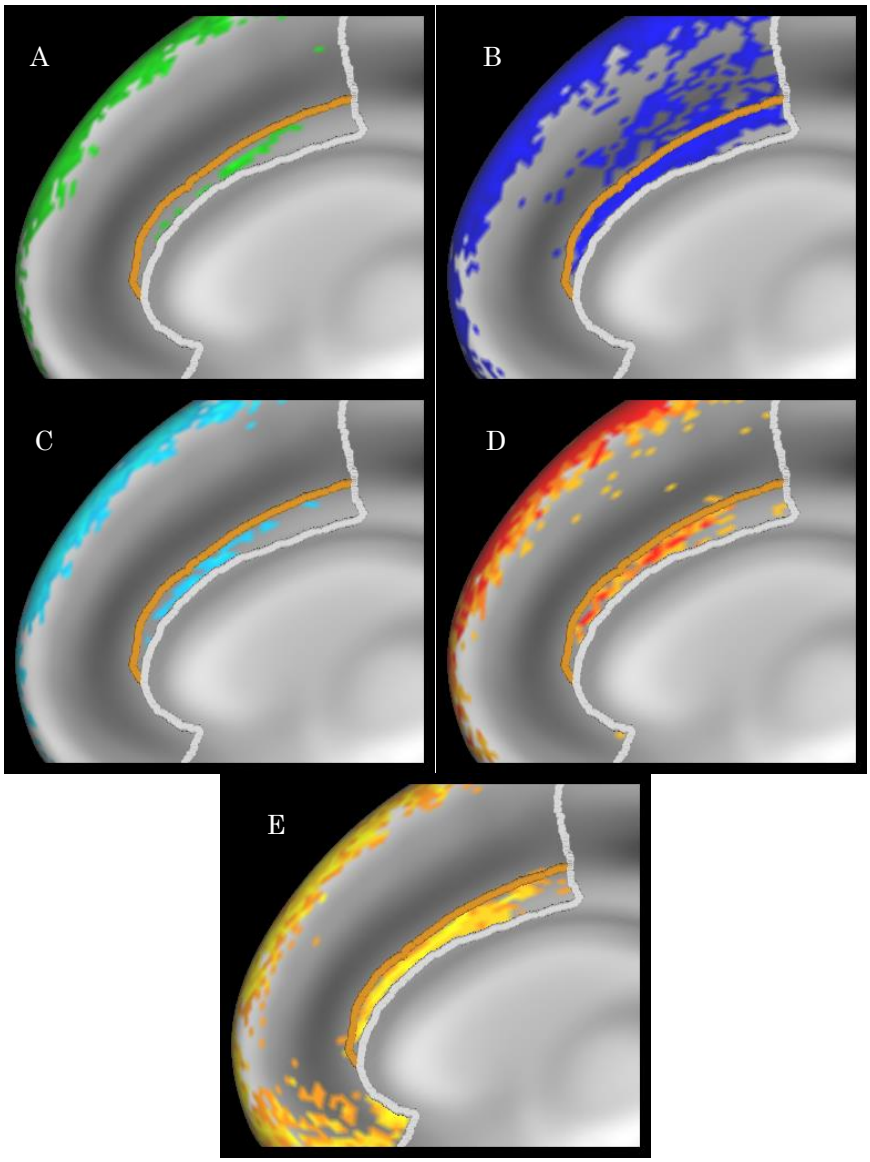


Figure 9. This "strong" border along the human cingulate sulcus (orange) is supported by connections from 5 secondary ROIs. A: Dorsal motor. B: Dorsal parietal. C: Temporal operculum. D. Ventral insula. E: Anterior temporal lobe.

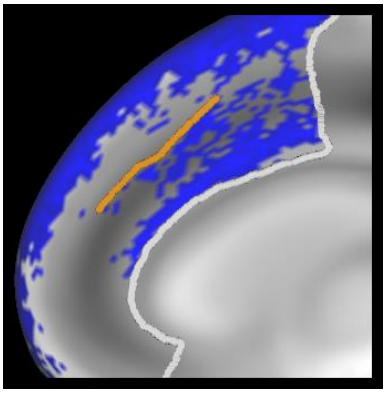


Figure 10. This "weak" border along the human paracingulate sulcus is supported by connections from the dorsal parietal secondary ROI.

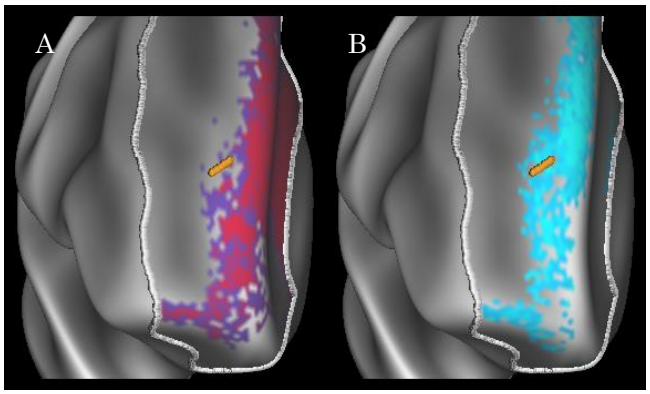


Figure 11. This ambiguous border crossing the superior frontal sulcus is supported by connections from the posterior precuneus (A) and temporal operculum (B) secondary ROIs.

Table 3. Analysis of border strengths within human extended dmPFC, along with justification for border strength ratings.

Border	Border Strength	Justification
1 DMR	Strong	Solid border formed by many connections
2 DMR	Strong	Solid border formed by may connections
3 Cingulate	Strong	Solid border formed by many connections
4 pDMR	Ambiguous	Solid border formed by only 2 out of 3 connections
5 pDMR	Strong	Solid border formed by many connections
6 FP	Strong	Solid border formed by many connections
7 vmPFC	Strong	Solid border formed by many connections
8 vmPFC	Ambiguous	Somewhat solid border only formed by 1 connection
9 FP	Strong	Solid border formed by 5 of 6 connections
10 DMR	Ambiguous	Connections end at slightly different places near border
11 DMR	Strong	Solid border formed by 4 of 5 connections
12 AM	Strong	Solid border formed by 2 connections
13 AM	Ambiguous	Solid border formed by 1 of 2 connections
14 AM	Ambiguous	Solid border formed by 1 of 2 connections
15 AM	Weak	Intermittent border formed by 1 connection
16 AM	Weak	Intermittent border formed by 1 connection
17 SFS	Strong	Solid border formed by many connections
18 SFS	Ambiguous	Connections end at slightly different places near border
19 SFS	Strong	Solid border formed by many connections
20 SFS	Strong	Solid border formed by many connections
21 SFS	Ambiguous	Connections end at slightly different places near border
22 Posterior	Ambiguous	Solid border formed by only 3 of 4 connections
23 FP	Ambiguous	Intermittent border formed by 2 connections
24 vmPFC	Strong	Solid border formed by many connections
25 Paracg.	Weak	Intermittent border formed by 1 connection

Some borders in human and chimpanzee extended dmPFC may be homologous based on the fact that they are share similar location and that their presence was inferred from the existence of homologous regions between the species (see parentheses beside the border names in the second column of

Table 2). There is most likely homology between 1 dorsomedial rim in humans and frontal-medial 4 in chimpanzees, which appear just inferior to the dorsomedial rim in both species. Frontal-medal 4 is supported by connections to homologs of VPM, DM, DPa, and PPr in humans. There is a similar case for 2 dorsomedial rim in humans and frontal-medial 2 in chimpanzees: the borders are in similar locations and they are supported by connections from all the secondary ROIs available in both species. Frontal-dorsal 1, located in the chimpanzee frontal pole, is supported by connections from homologs to VI, TO, ATL, DM, DPa, PPr, and APr in humans, showing striking similarity in location and supporting connections to 9 frontal pole, 7 vmPFC, and 8 vmPFC in the human frontal pole. Chimpanzee frontal-dorsal 5 shows similarity in location and connection to human 19 SFS, sharing connections to homologs of human VPM, DM, and DPa.

Cingulate also shows similar connections between humans and chimpanzees. On the other hand, chimpanzee frontal-dorsal 3 is located in a similar region to human 6 frontal pole and 23 frontal pole, but it is only supported by chimpanzee ATL (homologous to human ATL), while 6 frontal pole is supported by a multitude of secondary ROIs not limited to ATL, and 23 frontal pole is supported by VPM and APr.

Connectivity patterns of parcels

We found three main zones of connections within the extended dmPFC region of interest in both species: the medial surface, the dorsomedial rim (the rim separating the medial wall of the cortex from the rest of cortex), and the superior frontal gyrus

lateral to the dorsomedial rim. With the exception of the cingulate gyrus, the medial surface of extended dmPFC showed connections to only the precuneus ROIs, which are also located in medial cortex. The cingulate gyrus showed connection to a variety of secondary ROIs on the lateral and medial surface of the cortex. The superior frontal gyrus showed connections to the dorsal and lateral ROIs. Meanwhile, the dorsomedial rim displayed connections to a rich variety of regions on the lateral and medial surface of the cortex, like the cingulate gyrus. Most of these connections spanned the length of the dorsomedial rim and extended past the frontal pole. Parcels' connectivity is illustrated in detail in Figure 12.

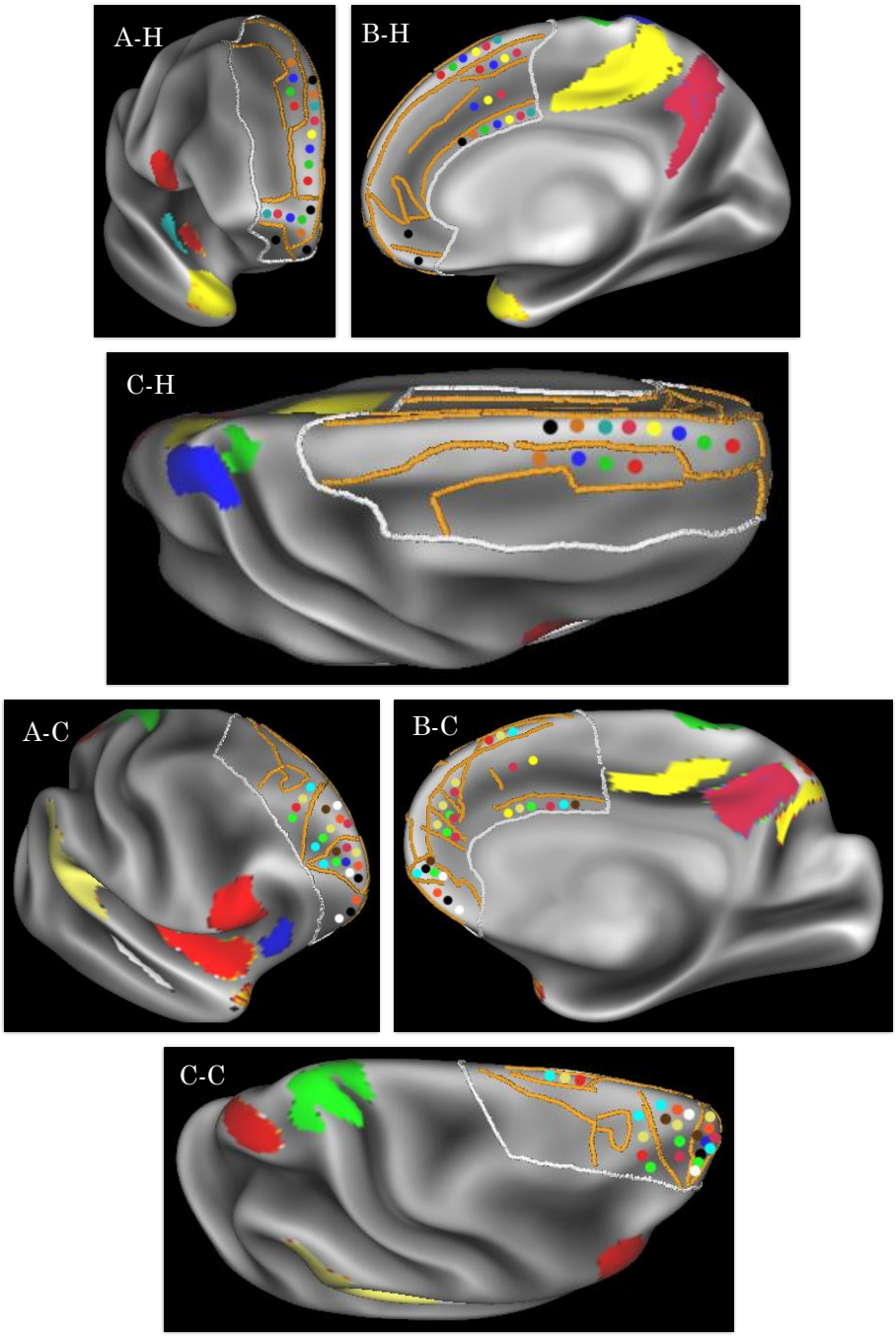


Figure 12. The connectivity of each parcel to secondary ROIs in humans (A-H, B-H, C-H) and chimpanzees (A-C, B-C, C-C), where "parcels" are spaces enclosed by borders within extended dmPFC. Colored dots represent the existence of probable connections from a parcel to a specific secondary ROI.
Key for humans: Red: VPM. Green: DM. Blue: DPa. Yellow: APr. Purple: PPr. Teal: TO. Orange: VI. Black: ATL.
Key for chimpanzees: Red: VPM. Blue: FOS. Orange: VI. Black: ATL. White: STS. Tan: TPJ. Light blue: SPL Green: DCS. Brown: POS Yellow: CgS. Purple: Pr.

On the other hand, the superior frontal gyrus lateral to the dorsomedial rim showed connections to the dorsal motor, dorsal parietal, and ventral insular ROIs. On the other hand, the middle frontal sulcus is a lacuna of probable connections to the secondary ROIs in humans. This is likely because this region was not included in the dmPFC ROI that we used to find the secondary ROIs (Figure 3). This may be the cause of the lacuna in the posterior lateral corner of extended dmPFC in chimpanzees as well.

Chimpanzees showed similar connectivity patterns to humans, but with several important differences. Like humans, the cingulate showed connections to most of the secondary ROIs while the most of the rest of the medial wall only showed connections to the precuneus and the adjacent parieto-occipital sulcus. However, unlike in humans, the anterior part of the medial wall showed connections to the precuneus, dorsal central sulcus, and temporo-parietal junction. Also, the dorsomedial rim does not show as clear a separation from the rest of the superior frontal sulcus in chimpanzees as it does in humans. Instead, connections are concentrated around four frontal regions that are less elongated than those in humans.

In order to more thoroughly compare connectivity-based parcels between humans and chimpanzees, we overlapped the outlines of the territories that showed probable connections to five sets of secondary ROIs common to humans and chimpanzees and compared the results from the two species (Figure 13). This increased the clarity of the similarity of the parcels in and near the cingulate,

frontal pole, and dorsomedial rim. If these parcels are actually homologous, then it is apparent that dorsomedial rim is elongated in humans compared to chimpanzees, and the frontal pole is enlarged (compared to the size of the rest of the brain) in chimpanzees compared to humans (relative to the size of the rest of the brain). There is considerable ambiguity in the location of the most lateral borders in humans.

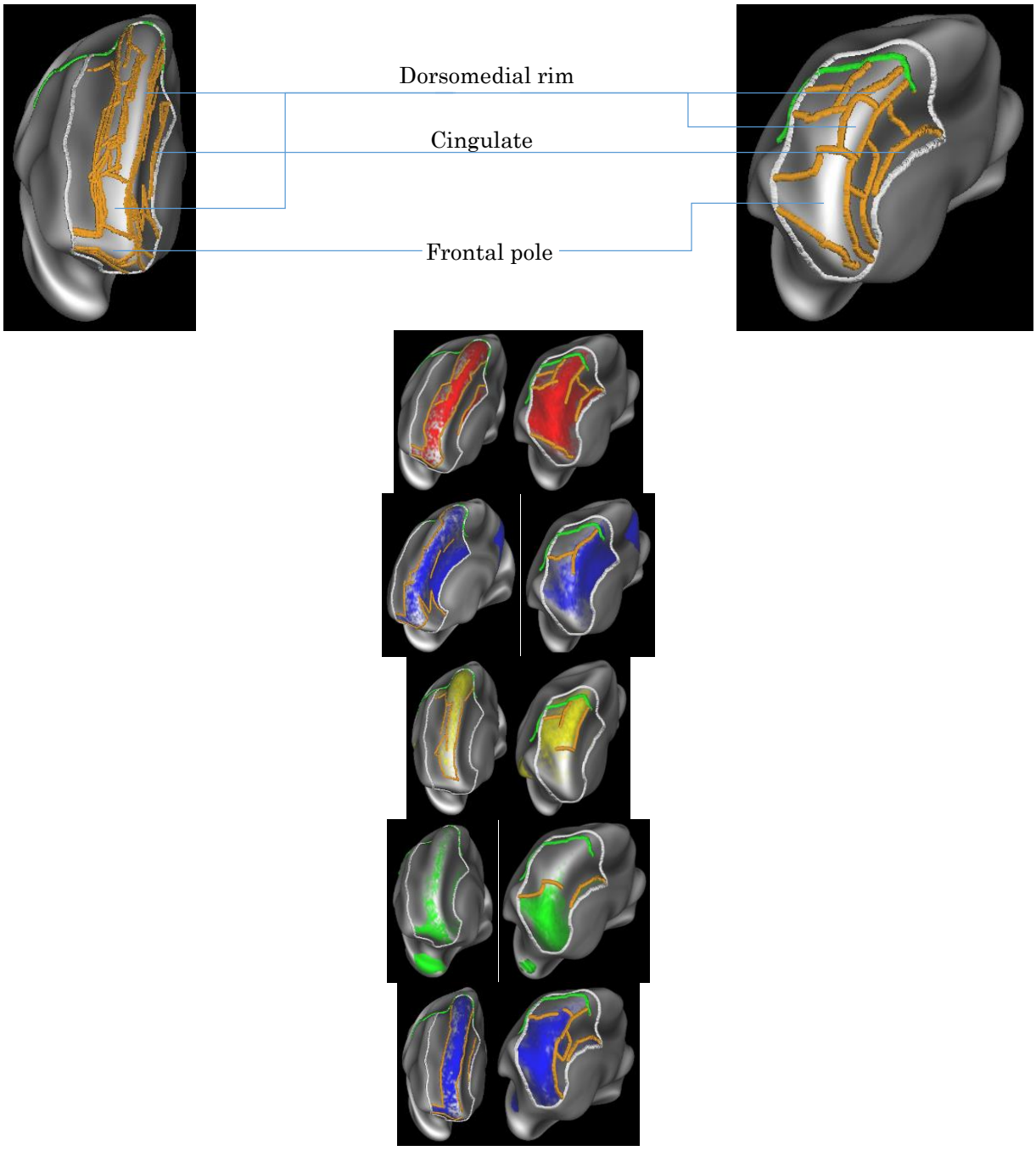


Figure 13. Human (left) and chimpanzee (right) borders show greater similarity in detailed analysis of connections from the secondary ROIs that they have in common (top). From the second-to-top to bottom, the borders of connections are shown from temporo-parietal junction, human posterior precuneus/chimpanzee precuneus, ventral premotor, anterior temporal lobe, and human temporal operculum and ventral insula/chimpanzee insula. Orange lines represent connectivity borders. The green line in posterior extended dmPFC is a myeloarchitectonic border that separates the sparsely myelinated frontal cortex from highly myelinated premotor cortex. The darker colors indicate more probable connectivity with the secondary ROI of interest. Solid colors were used to display the connections for clarity.

Once we had a human TPJ secondary ROI, we compared the overlap between the connections from it and from the posterior precuneus to the overlap between connections from TPJ and precuneus in chimpanzees in extended dmPFC (Figure 14). TPJ and precuneus are two regions considered unambiguously part of a "social brain network" in humans and chimpanzees. This analysis revealed an enlongated region of connections in the dorsomedial rim and frontal pole in humans, while the overlap in chimpanzees occurred in a large cluster in the anterior medial part of extended dmPFC.

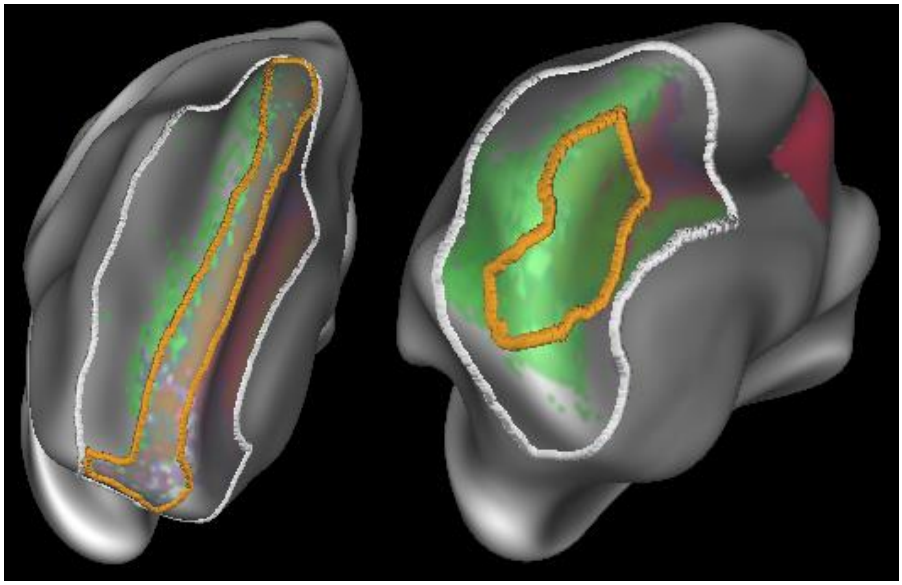
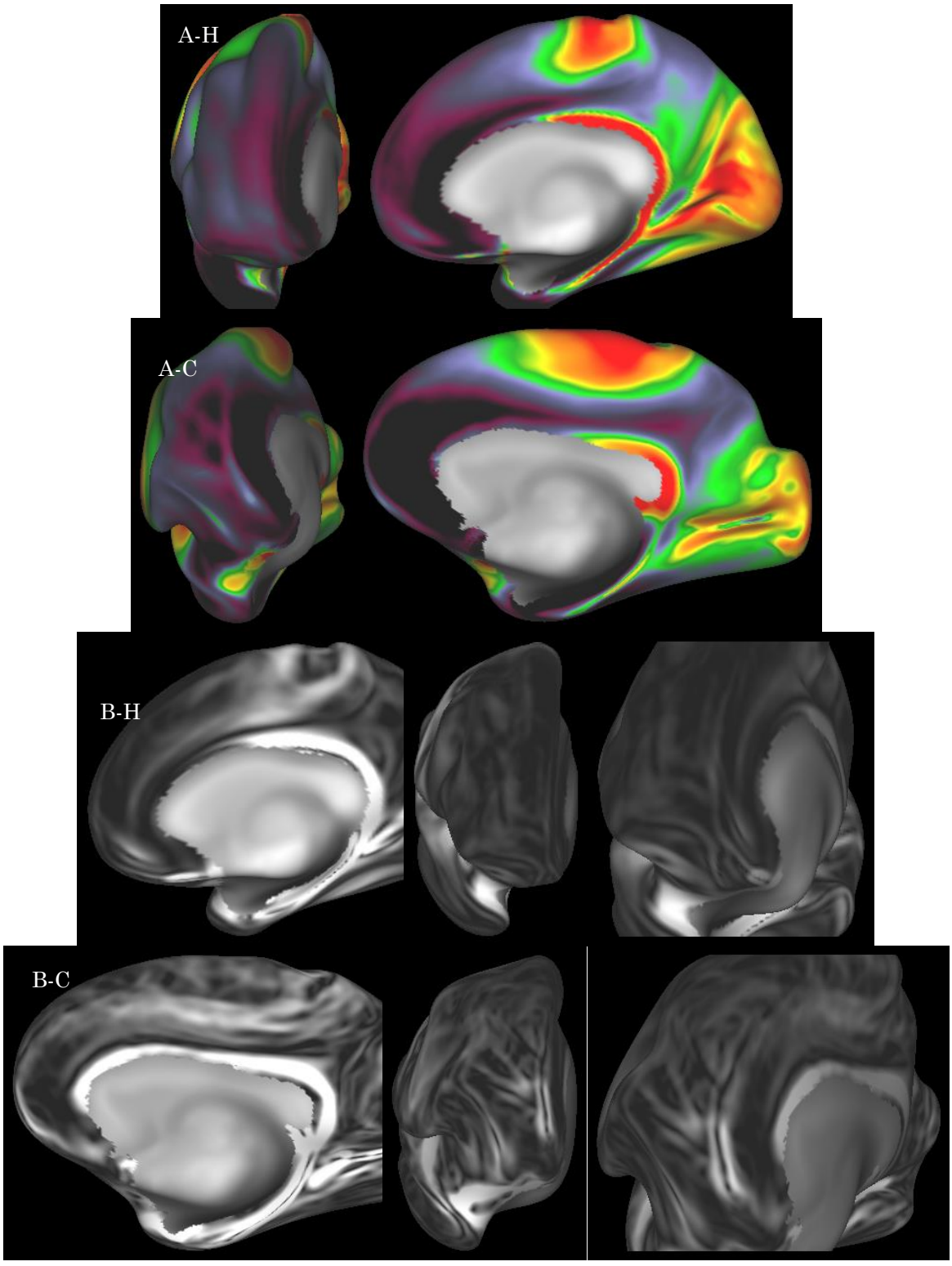


Figure 14. Overlap of precuneus (purple) and temporo-parietal junction (green) in humans (left) and chimpanzees (right). The region of overlap is denoted the orange outline, The overlapping region falls mainly along the dorsomedial rim in humans, but is more clustered toward the anterior extended dmPFC in chimpanzees.

Comparison of connectivity borders to myeloarchitectonic borders

We drew myeloarchitectonic borders based on locations that exhibited high rates of change in cortical myelin content (Figure 15B-H, B-C). Human connectivity borders

show remarkable similarity in location to myeloarchitectonic borders (Figure 15C-H). This is not as apparent in chimpanzees, especially on the lateral portion of extended dmPFC. However, some of the chimpanzee connectivity borders that show high homology with human connectivity borders also show similarity to myeloarchitectonic borders (Figure 15C-C). These include frontal-medial 2 and 4 (possibly homologous to human 1 and 2 dorsomedial rim, respectively), frontal-dorsal 6 (possibly homologous to human 9 frontal pole, 7 vmPFC, and 8 vmPFC), and frontal-medial 3 (possibly homologous to human 7 vmPFC and 8vmPFC).


A-H
A-C
B-H
B-C

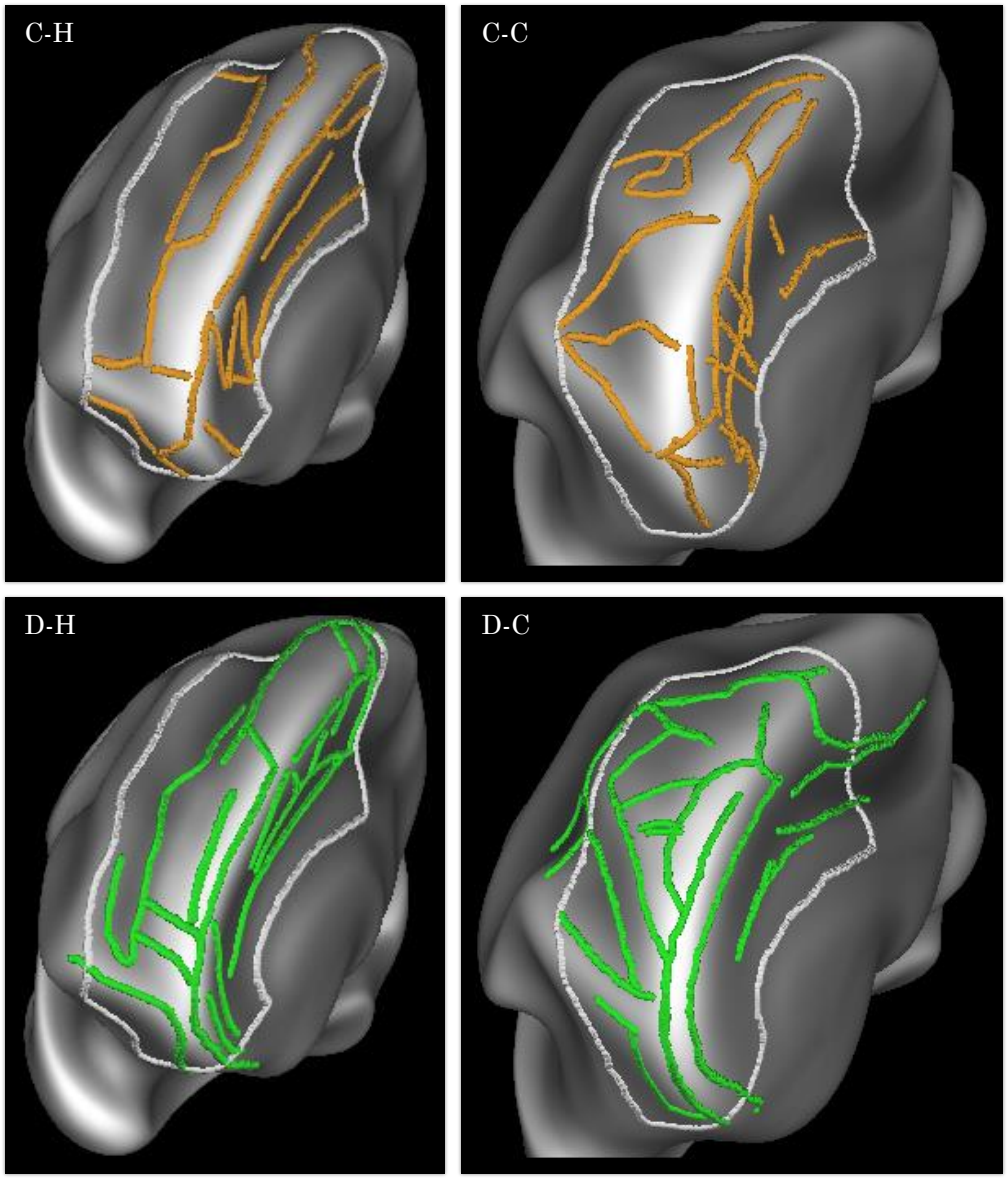


Figure 15. Myeloarchitetonic borders show similarity with structural connectivity. **A:** Myelin map of human (A-H) and chimpanzee (A-C) cerebral cortex (Glasser and Van Essen 2011). Warmer colors represent higher cortical myelin content. Note that primary cortex has higher cortical myelin content than association cortex. **B:** Myelin gradient map of the rate of change of cortical myelin content in human (B-H) and chimpanzee (B-C) cortex. Lighter colors represent higher rates of change of myelin content. Regions of high rates of change in myelin content were used to draw the myeloarchitectonic borders in green in Figure 15C. Myelin borders in chimpanzee cortex do not appear as smooth as borders in human cortex because they are the average of only 29 subjects (versus approximately 440 subjects for humans). **C:** Note the substantial overlap between myeloarchitectonic borders (green) with structural connectivity borders in humans (in orange, Figure 6) (C-H, D-H). While myelin borders do not overlap as well with connectivity borders in chimpanzee cortex, there is still a clear similarity in the dorsomedial rim (C-C, D-C).

Discussion

Location of borders

In our study, we parceled a region of dorsal and medial frontal cortex which we call "extended dmPFC" by finding and delineating borders. Sallet et al. (2013) and Neubert et al. (2014) conducted studies on the structural connectivity of a similar region in humans. Their cl1, cl2, and cl3 clusters appear to occupy the parcel delineated by our 1 DMR, 4 posterior DMR, 10 DMR, and 11 DMR borders (Figure 6). However, a full comparison between their results and ours is only possible where their regions of interest overlap with ours.

The dorsomedial rim appeared longer and more clearly defined in humans than in chimpanzees. We observed few borders perpendicular to the dorsomedial rim in humans. For a long stretch, the dorsomedial rim in humans continues uninterrupted. While this might be evidence for the enlargement of dorsomedial rim in humans compared to chimpanzees, the lack of coronally oriented borders is suspicious and begs further study, especially since coronally oriented borders were identified in Mars et al. and Sallet et al. However, coronally oriented myeloarchitectonic borders were also uncommon in humans, so this linear pattern parallel to dorsomedial rim may be a common theme in the structural organization of human dorsal frontal cerebral cortex.

Of note is the consistency between the location of functional activation of dmPFC in Mitchell et al. (2006) (Figure 2A) and in meta-analyses of regions that show functional activation during social cognitive tasks (Bzdok et al. 2013; Li et al.,

n.d.) (Figure 2B, Figure 3), all of which are studies of humans. All three studies define dmPFC activations as starting approximately halfway down the dorsomedial rim and extending to just posterior to the frontal pole. These studies' dmPFC activations lie within a region of extended dmPFC that shows highly probable connections to every secondary ROI in humans. In particular, Li et al.'s dmPFC follows our borders in extended dmPFC closely, showing that our structural borders *do* coincide with known functional borders in this particular region (Figure 16).

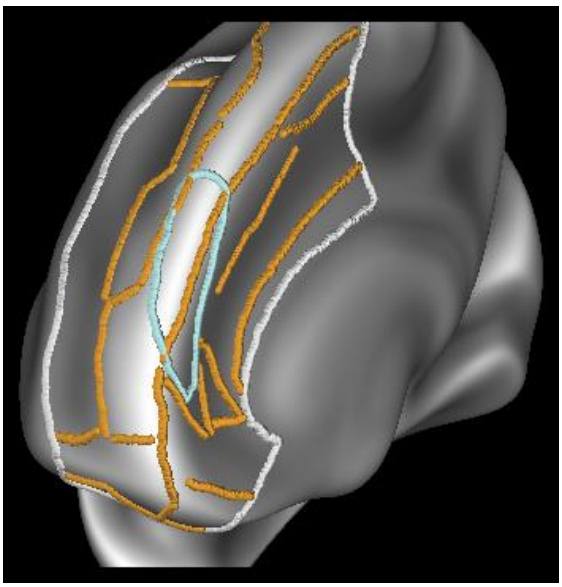


Figure 16. Connectivity borders within extended dmPFC (orange) overlaid with the border of dmPFC as found in Li et al. (n.d.).

These studies' dmPFC activations may be a nexus of connectivity within the dorsal and medial frontal cortex that act as a functional module for certain kinds of social cognitive tasks. The exact tasks have yet to be determined. While it was previously hypothesized that dmPFC was a node for theory of mind, Saxe and Kanwisher showed that medial prefrontal cortex does not show selective activation for inferring others' mental states (Saxe and Kanwisher 2003). On the other hand,

one study to date (Williams et al. 2005) supports Saxe's hypothesis that the dmPFC is a node for triadic attention (Saxe 2006). For now, this is the closest we can come to defining "the" dmPFC as an area in light of the unclear evidence and conflicting hypotheses of its function. However, now that we also have extensive data on the location of connectivity borders in chimpanzee extended dmPFC, we can test the hypothesis that the peak functional activation of dmPFC for social cognitive tasks will occur in a dorsomedial region of chimpanzee cortex that shows highly probable connections to each secondary region of interest (ROI) in chimpanzees.

Comparing parcels

In both species, we saw a general pattern of medial secondary ROIs connecting to medial regions of extended dmPFC, dorsal and lateral ROIs connecting to lateral regions of extended dmPFC, and connections from a variety of ROIs connecting to the dorsomedial rim (Figure 12). The dorsomedial rim was longer and narrower in humans, while the frontal pole appeared larger in chimpanzees (relative to total cortical surface size). Human connectivity borders showed greater alignment with myeloarchitectonic borders than chimpanzee connectivity borders, although the least ambiguous chimpanzee borders do align well with myeloarchitectonic borders. This effect may be due to low sample size in chimpanzees. In this analysis, species differences were more based on the position and structure of parcels than on the connectivity patterns of parcels.

We observed a small lacuna in the middle frontal gyrus of chimpanzees, and a long lacuna along the middle frontal gyrus of humans. The lacuna in humans may

reflect the fact that our original, smaller dmPFC ROI did not extend to middle frontal gyrus (Figure 3). Figure 3 shows that while regions immediately inferior to dmPFC (including the cingulate gyrus) showed highly probable connections to the original dmPFC ROI, these connections abruptly ended along the superior frontal sulcus. Curiously, this linear lacuna is interrupted a band of highly probable connections to a variety of secondary ROIs in the frontal pole. However, ventral to the frontal pole, the lacuna continues into the ventrolateral section of extended dmPFC. On the other hand, territories inferior to the cingulate sulcus that were left out of the original dmPFC ROI still showed probable connections to some secondary ROIs. This was especially true for the cingulate gyrus, even though it was not included in the dmPFC ROI that was used to find the secondary ROIs. Therefore, the dmPFC ROI has more probable connections to areas immediately medial to it than areas immediately lateral to it. This should come as no surprise, since dmPFC shows tight connections to anterior cingulate cortex (Mundy 2003). Thus, the frontal medial surface of cortex, dorsomedial rim, frontal pole, and superior frontal gyrus, and excluding middle frontal gyrus and the ventrolateral part of extended dmPFC, might be a major structurally connected network within frontal cortex (Figure 17).

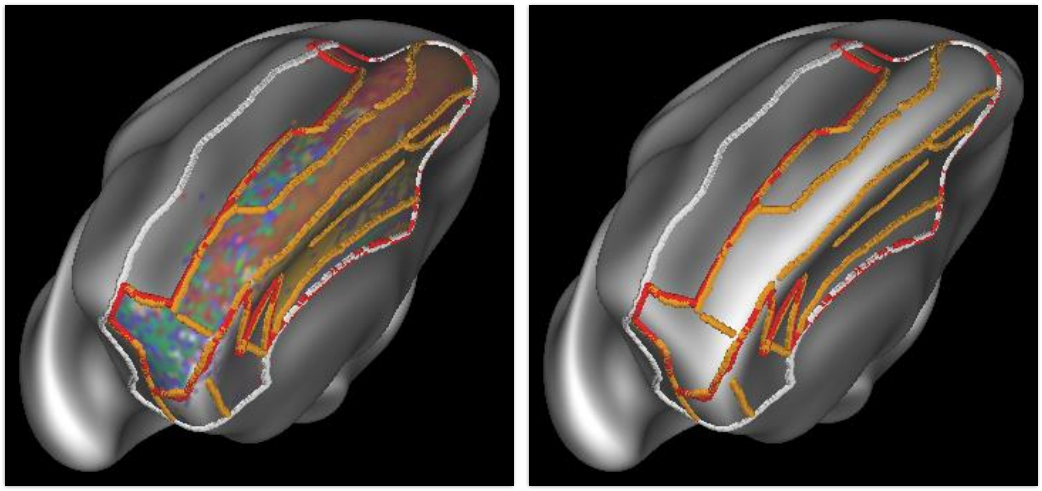


Figure 17. The medial frontal surface of cerebral cortex, dorsomedial rim, frontal pole, and superior frontal gyrus may be a contiguous, tightly bound network in humans.

Unexpected connections

Connections from the dorsal motor (DM) and dorsal parietal (DPa) secondary ROIs extend along the entirety of the dorsomedial rim (Figure 18). In humans, these connections extend past the frontal pole into ventromedial prefrontal cortex. In chimpanzees, these connections stop at the frontal pole. Either way, this is completely unexpected, as DM and DPa are located squarely in primary motor and primary somatosensory cortex, respectively. (To be specific, DM lies within the foot representation in the motor homunculus and DPa lies within the hip representation in the somatosensory homunculus.) On the other hand, extended dmPFC is located entirely in association cortex, and mostly contains regions associated with the "highest" cognitive functions, such as cognitive control, and the ROI was specifically drawn to *avoid* primary cortex.

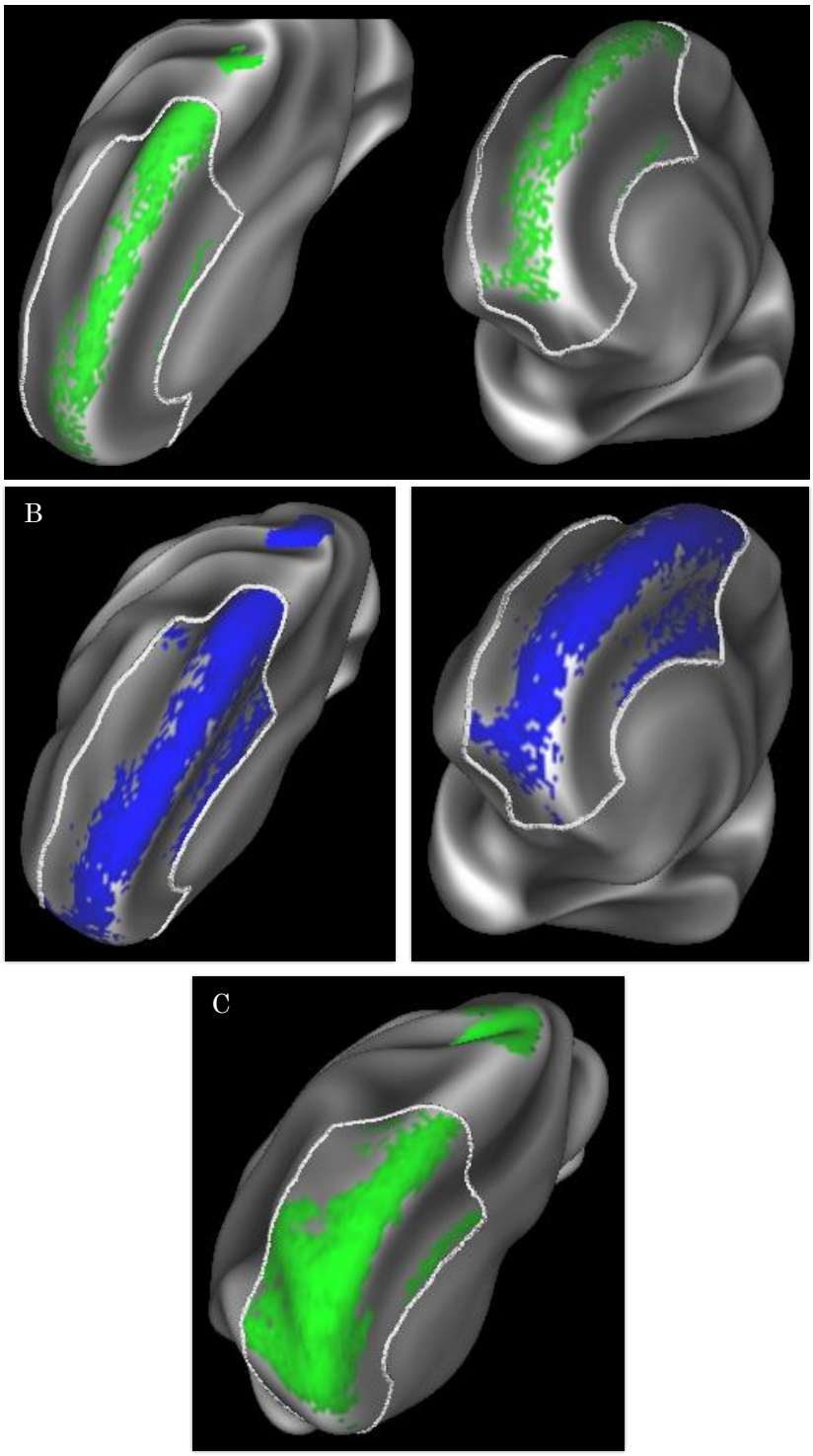


Figure 18. Connections from the dorsal motor (A) and dorsal parietal (B) secondary ROIs extend down the dorsomedial rim and superior frontal gyrus past the frontal pole in humans, even though this region is part of primary motor cortex. Similar connections are visible from the chimpanzee dorsal central sulcus ROI (C).

The most probable explanation for these connections is a false positive. DTI can pick up false positives from crossing fiber tracts. In this specific case, DTI may be detecting the connections from the corticospinal tract, which projects from primary motor and somatosensory areas, and that intersects with fibers to prefrontal cortex. It is unlikely these connections visible in extended dmPFC are premotor regions because DM and DPa show highly probable connections to parts of dmPFC as far anterior as the frontal pole and vmPFC, which are clearly not premotor cortex.

The other possibility, however, is that the results reflect actual connectivity. This possibility is highlighted by the fact that when we query the resting state functional connectivity data in the HCP440 dataset, we find anticorrelations between activity in both DM and DPa and the dorsomedial rim. It is completely unexpected that some brain areas *known* to encode some of the most basic sensory and motor processes be connected to regions associated with some of the "highest" cognitive functions, such as cognitive control. In a strange play on embodied cognition, could this mean that body representations are important for cognitive control? Could this mean that these regions of primary motor and primary somatosensory cortex are also hubs for other activity? Or does this mean that DM and DPa are in fact not parts of motor and somatosensory cortex at all? If these connections are not false positives, then this has profound implications for the study of prefrontal cortex. Further investigation is warranted to settle this question.

Further study

For the sake of completeness, we would like to perform a comparative study that includes humans, chimpanzees, and rhesus macaques (*Macaca mulatta)*. Macaques are anthropoid primates, like humans and chimpanzees, but unlike humans and chimpanzees, they are not hominids. Therefore, macaques can serve as an outgroup species that can help us determine which connection patterns are human specialties, which patterns are chimpanzee specialties, and which patterns are likely common to all anthropoid primates. We intend to parcel macaque dorsal and medial frontal cortex with some modifications to the border-finding technique we used in this study.

In humans, we found secondary ROIs by tracking from our original dmPFC ROI to its inverse. Using the same strategy on the chimpanzee dataset required higher thresholds for the probability threshold in order to find discrete clusters of connections that we could label as secondary ROIs. On the other hand, preliminary analysis of the Yerkes macaque dataset indicates that we will need to loosen the threshold for the probability of least hindrance to diffusion in order to find secondary ROIs in macaques. The visibility of connections at a given threshold has as much to do with individual and species differences as it has to do with scanning conditions. This may explain why several connections to inverse dmPFC showed up in chimpanzees but not in humans. This led to the delineation of secondary ROIs in the superior temporal sulcus, TPJ, superior parietal lobule, and fronto-orbital sulcus (FOS) in chimpanzees, which were not visible in humans. (While the FOS as

a structure does not exist in humans, we did not observe connections in or around ventromedial prefrontal cortex in humans, near where FOS is located in chimpanzees.).

Therefore, we propose a new method for further study of the connectivity of dmPFC that can be used across all three species. Instead of tracking from dmPFC to its inverse and then tracking from the secondary ROIs to extended dmPFC, we propose tracking from extended dmPFC to ROIs in the parietal lobe, temporal lobe, and the rest of the frontal lobe not included in dmPFC. This method should increase the likelihood that we will find regions of contiguous connections that we can label as secondary ROIs in macaques, regardless of the threshold for the probability threshold. This same approach will be repeated in humans and chimpanzees for consistency. Using this approach on the will also allow us to fill in gaps in connections, and may help resolve the ambiguous border between superior frontal gyrus and middle frontal gyrus in humans (Figure 13).

Possible Sex Differences

In this study, the human and chimpanzee dataset was drawn entirely from females of both species. Ideally, any such study would contain data from males and females and would analyze the data from each sex separately in order to account for possible sex differences. For instance, the Human Connectome Project dataset contained scans from males and females across from an ethnically and socioeconomically diverse range of humans to ensure that the results reflected the diversity of the general U.S. population. However, our sample size came under time and budgetary

constraints, so we chose one sex to limit our sample size while still making valid interspecies comparisons. Considering the ramifications of this study and other connectivity studies to dementia, we chose females for our human dataset because dementia is more common in females than in males. Correspondingly, we chose females for our chimpanzee dataset in order to increase the validity of the interspecies comparisons. A result of this is that our findings are more valid for females than for males. The converse would also be true had we performed our study using data only from males.

Applications

Noninvasive structural mapping of cerebral cortex is currently of great interest in neuroanatomy. Anatomical studies of the brain were originally limited to cytoarchictectonic and tract-tracing studies. These studies tract-tracing studies are slow and can only be done in nonliving subjects. Therefore, for ethical reasons these kinds of invasive studies are mostly performed in sacrificed nonhuman primates or in humans and other primates that had died of natural causes. Glasser et al. (2011) propose that structural connectivity information could be one part of a multimodal effort to parcel cerebral cortex *in vivo*. This would allow researchers to localize structural regions *in vivo* in cerebral cortex, which would be a huge advancement in neuroanatomy. Doing so would greatly increase the pace of detailed anatomical studies because they would be done on living individuals with the aid of computer visualization software. Sacrificing subjects would become less necessary for detailed neuroanatomical knowledge. Such a revolution would open up more anatomical

studies to humans, reducing the need for the use of nonhuman primate brains as just a model for the human brain (although the study of nonhuman primates would remain relevant to neuroanatomy for comparative purposes). Also, it would become possible to localize lesions or functional activations to a living individual's specific anatomically defined regions. Further detailed studies of myeloarchiture and structural connectivity from noninvasive sources such as MRI may be able to provide researchers with anatomical maps as detailed as the Brodmann maps of cytoarchictonic regions.

Connectivity data are also relevant to the study of neurodevelopmental disorders. This is especially true for autism spectrum disorder, a neurodevelopmental disorder that is behaviorally characterized by the hindered ability of affected persons to communicate and interact with others. Neurologically, autism can be characterized in part by abnormalities in connectivity, but there is disagreement over whether autistic brains are functionally and structurally hyperconnected, hypoconnected, or some specific combination of the two (Courchesne and Pierce 2005). Recent evidence, such as greater white matter volume in frontal cortex (Carper et al. 2002) and increased resting state functional connectivity (Supekar et al. 2013), suggests an emphasis on hyperconnectivity. This is of particular importance to studies of dmPFC because of dmPFC's links to social cognition. Autistic individuals have trouble engaging in joint attention, which appears to be necessary for collaboration, and which might be mediated by dmPFC. Comparing structural and functional connectivity between autistic and typically

developing individuals will be a necessary part of determining the exact abnormalities in connectivity that contribute to symptoms of autism, and of determining the mechanisms that support social cognitive abilities in typically-developing individuals that autistic individuals have difficulty with. A study using an approach similar to ours might reveal that the parcels within extended dmPFC show altered connectivity to those of typically-developing individuals, and the degree and/or of difference may be correlated with an autistic individual's specific deficits—or it may even find different connectivity-based parcels altogether.

Conclusion

The dorsomedial prefrontal cortex is a region of cerebral cortex that shows functional activation during social cognitive tasks in humans and chimpanzees. Over the course of this study, we have proposed new methods for parceling cortex based on searching for borders of connectivity. Using this approach, we discovered three apparently homologous regions in humans and chimpanzees within the vicinity of dmPFC: dorsomedial rim, frontal pole, and cingulate cortex. The parcels that resulted from these borders conform to the borders of dmPFC as identified by functional activation studies and meta-analyses of brain regions involved in social cognition. While our approach does require refinement, we believe that these structural connectivity maps, along with other anatomical methods derived from neuroimaging, can provide the basis for the development of anatomical maps of cerebral cortex derived through noninvasive means.

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