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Comparative Primate Connectomics

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Keywords

Connectivity · Diffusion-weighted imaging · Functional MRI · Tractography

Abstract

A connectome is a comprehensive map of neural connections of a species nervous system. While recent work has begun comparing connectomes across a wide breadth of species, we present here a more detailed and specific comparison of connectomes across the primate order. Long-range connections are thought to improve communication efficiency and thus brain function but are costly in terms of energy and space utilization. Methods for measuring connectivity in the brain include measuring white matter volume, histological cell counting, anatomical tract tracing, diffusion-weighted imaging and tractography, and functional connectivity in MRI. Comparisons of global white matter connectivity suggest that larger primate brains are less well connected than smaller primate brains, but that humans have more connections than expected for our cortical neuron number, which may be concentrated in the prefrontal cortex. Although there is significant overlap in structural connectivity between humans and nonhuman primates, human-specific connections are found in cortical areas involved with language, imitation, and tool use. Similar to structural connectivity, there is also widespread overlap between humans and macaques in resting state functional connectivity. However, there are again a number of human-specific connections in cortical regions involved in language, tool use, and empathy. Comparative connectomics also offers the opportunity to detect specializations of connectivity in other primate species besides humans. Future research should capitalize on the ability of diffusion tractography to measure connectivity in postmortem brains that could expand the representation of species beyond humans, chimpanzees, and rhesus macaques, and facilitate identification of connectivity-based adaptations to different social and ecological niches. This work will require careful attention to establishing cortical homologies across species and to improving tractography methods to limit detection of false-positive and false-negative connections. Finally, it will be important to attempt to establish the functional significance of variation in connectivity profiles by examining how these covary with behavior and cognition both across and within species.

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Introduction

One approach to learning about human brain evolution is to compare the human brain with the brains of other living primate species. The logic of this approach is that if we can identify a characteristic of the human brain that is not present in the brain of any other living primate species, then we can infer that the trait evolved in our lineage after we diverged from a common ancestor with chimpanzees approximately 7 million years ago [Langergraber et al., 2012]. Note that any conclusion about human brain evolution using this approach in particular depends upon comparisons with our closest living primate relatives, the two species within the genus *Pan*: chimpanzees and bonobos. A great deal of research has been focused on detailed comparisons of cortical gray matter size between humans and macaque monkeys [Van Essen and Dierker, 2007]. Other studies have focused on cortical gray matter comparisons among a broader array of primate species, including chimpanzees. These studies have revealed that the human brain has larger association cortices relative to primary sensory and motor cortices when compared with nonhuman primates [Rilling, 2014]. In this review, we instead focus specifically on the white matter beneath the cerebral cortex, which includes the axons that project to and from neurons found in gray matter. A connectome is a comprehensive map of neural connections of a species nervous system [Sporns et al., 2005]. While recent work has begun comparing white matter connectomes across a wide breadth of species [van den Heuvel et al., 2016], here we focus on a more detailed and specific comparison of connectomes across the primate order.

Before considering how connectivity varies across human and nonhuman primate brains, it is useful to consider the costs and benefits of white matter connections. Their benefit is that they distribute and integrate information across brain regions, and provide the organism with a unified sense of consciousness. Their costs however include the energy needed to build the connections during development, the energy needed to maintain their proper functioning, and the space they require. While gray matter consumes more energy than white matter [Yu et al., 2017], the metabolic demands of white matter are still significant. In gray matter, most energy is used for synaptic activity, whereas in white matter, most energy is used to operate the sodium and potassium pumps that maintain electrochemical gradients across the axon membrane [Yu et al., 2017]. These costs may place limits on the number of neuronal connections that the organism can metabolically support. Spatial constraints may also impose limits on connectivity. In humans, for example, head and therefore brain size may be constrained by the size of the birth canal through which the head must pass [Trevathan and McKenna, 1994] and by the need to balance the head over our center of gravity when standing bipedally. There are an estimated 16 billion neurons in the human cerebral cortex [Herculano-Houzel, 2009]. In a maximally connected network, each neuron would therefore be connected to about 16 billion other neurons. However, in reality, a given neuron has only about 1,000–10,000 connections [Pakkenberg et al., 2003], indicating that our brains are quite sparsely connected at the neuron-to-neuron level. Brains can minimize costs by minimizing the number of connections among neurons; however, this results in low "communication efficiency," defined as the number of steps required to travel from one node (i.e., neuron) to another in a network. An efficient network distributes and integrates information quickly (i.e., only a few steps needed to send information from one place to another) and is expected to provide the organism with improved information processing. For example, efficiency of structural connectivity is positively correlated with intelligence quotient in human brains, and the efficiency of functional networks increases across development [van den Heuvel et al., 2009; Hagmann et al., 2010].

To illustrate the relationship between network cost and efficiency, we can imagine a hypothetical brain network composed of 7 rows of 5 neurons each (Fig. 1), and we can ask how many steps it takes to get from the upper left to the lower right node of the network. One way to wire this network is to connect the upper left node with every other node in the network (Fig. 1a). This is a "star" network with high global efficiency because it requires just 1 step to go from the upper left node to the lower right node, and just 2 steps to travel between any other pair of nodes. However, it is also a costly network in terms of configurations, as it requires a large number of long-range connections. Brains are not wired like this, presumably because the cost is intolerable, and because this type of network topology involves high vulnerability to damage to the central nodes. Alternatively, we can connect the network with lower cost including only short connections between neighbors, resulting in a network with low cost, but also with low efficiency. In Figure 1b, all connections are short, but it requires 34 steps to get from the node in the upper left to the node in the lower right. In reality, nervous systems tend to be wired according to a trade-off between forces that aim to minimize total wiring, and

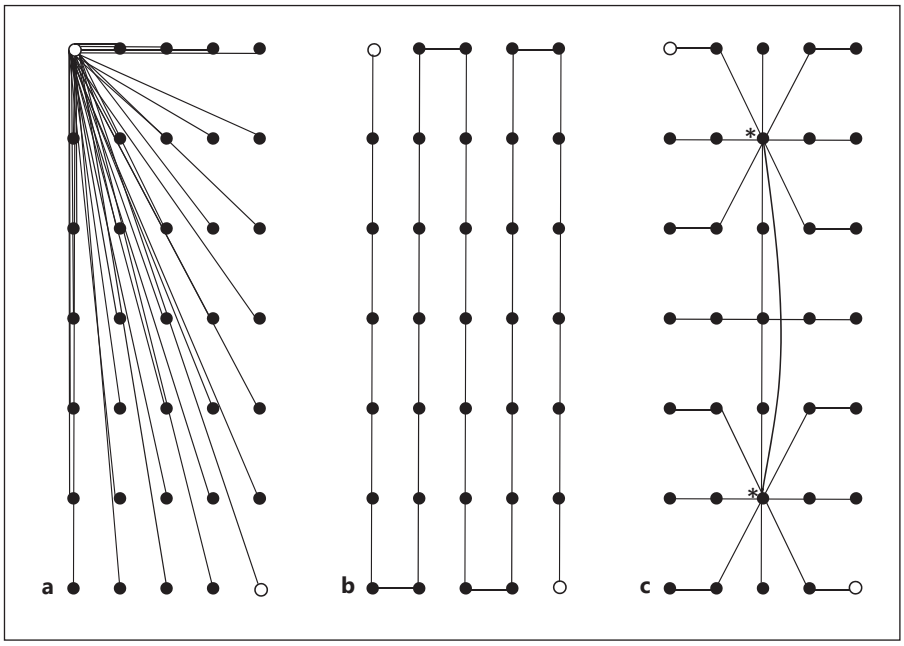

Fig. 1. The cost of building an efficient network. **a** A network in which the upper left node is connected to every other node and path length to the lower right node is 1; efficiency is high. **b** A minimally efficient and minimally connected network in which it requires 34 steps to get from the upper left to the lower right node. **c** A small-world network that perseveres efficiency with minimal costs; only 5 steps are required to get from the upper left to the lower right node.

forces that aim to strive for high global communication efficiency, together providing a balanced network architecture with a high level of local circuitry (to preserve wiring) and locally clustered subcommunities, together with the presence of a few but expensive global shortcuts that enable efficient global communication [Bullmore and Sporns, 2012]. These global shortcuts have been argued to be centralized around the formation of a few centrally embedded hub nodes in the network, forming a network architecture of locally connected modules that are sparsely connected with other modules by means of centrally connected hubs. The sparse long-distance, intermodule connections are of high cost in terms of their projection distance, but they are crucial for preserving efficiency across the brain. In the network architecture shown in Figure 1c, the formation of mostly local circuitry enforces the formation of 2 local subgraphs in the network, while global shortcuts between richly connected hub nodes (marked with asterisks) ensure that only 5 steps are needed to get from the upper left to the lower right node.

Methods for Measuring and Comparing Connectivity in Primate Brains

At the most basic level, the volume of white matter can be used as a crude estimate of the total number of connections a brain has and can be easily calculated from a structural MRI scan. At a more detailed level, histology can be used to estimate the number of glial cells in the brain. The number of oligodendrocytes, one type of glial cell, is believed to be proportional to total axon length [Herculano-Houzel et al., 2010]. In the corpus callosum, histology can be used to estimate the total number of interhemispheric axons since all of the axons are traveling in the same mediolateral direction [Phillips et al., 2015].

In addition to these measures of global connectivity, methods are available to track specific connections. The gold standard method is to inject anterograde or retrograde tracers into a brain area while the animal is living and then observe where the tracer is transported to postmortem [Kobbert et al., 2000]. This allows reconstruction of white matter fiber tracts [Schmahmann et al., 2007; Petrides and Pandya, 2009]. Many such studies have been done in monkeys [Modha and Singh, 2010; Markov et al., 2013], but these methods cannot be applied in humans or great apes due to their invasive nature. Fortunately, noninvasive neuroimaging techniques have been developed that enable tracking of white matter connections in humans and great apes.

One such technique is diffusion-weighted imaging (DWI) combined with tractography [Basser and Jones, 2002; Beaulieu, 2002; Mori et al., 2002; Parker et al., 2002; Behrens et al., 2007]. DWI aims to measure the diffusion of water in the brain. Bound by the axonal structure, water molecules will preferentially diffuse parallel to rather

than perpendicular to the direction in which axons are oriented. Thus, by estimating and following the principal direction of water diffusion across voxels, the trajectory of fiber tracts can be estimated. Importantly, tractography can be done either in vivo or postmortem, which potentially vastly expands the range of species that can be studied with these methods. Although fixation of postmortem brains decreases the diffusion signal [D'Arceuil and de Crespigny, 2007], this can be recovered with longer scan durations. Tractography has certain limitations that currently make it vulnerable to both false-positive and false-negative connections. It has difficulty reconstructing correct diffusion directions in white matter voxels of complex fiber architecture such as crossing and "kissing" fibers. It also has a known bias for detecting connections that reach cortical gyri as opposed to sulci [Li et al., 2012; Jbabdi et al., 2015; Donahue et al., 2016]. Nevertheless, several studies have reported reasonable correspondence between tracer and tractography results for macaque monkeys [Dauguet et al., 2007; Dyrby et al., 2007; Schmahmann et al., 2007; Jbabdi et al., 2013; van den Heuvel et al., 2015].

Functional connectivity can also be measured noninvasively with fMRI. Functional connectivity measures temporal correlations of blood oxygen level-dependent activation in anatomically separated cortical regions at rest [Biswal et al., 1995; Greicius et al., 2003]. It provides a different type of connectivity as provided by tract tracing and diffusion tractography, as the "connections" identified by fMRI can be multisynaptic and interpreted to reflect levels of synchronization between activity patterns of regions rather than direct anatomical connections.

One challenge inherent to comparing primate connectomes with these methods is to define homologous cortical areas across species. While significant progress has been made in establishing the homologies between humans and macaque monkeys [Van Essen et al., 2016], less work has been done with other primate species, including our closest living relative, the chimpanzee.

Comparisons of Structural Connectivity

MRI/Histology

Comparative morphometric studies using MRI have established that white matter volume scales with positive allometry on cortical gray matter volume. In other words, as primate brains get larger, white matter increases in size faster than does cortical gray matter [Rilling and Insel, 1999b]. As a result, larger primate brains have proportionately more white matter than smaller primate brains. One well-known paper argued that an allometric slope of 1.23 would correspond to a situation in which a constant fraction of cortical neurons send axons into white matter across species [Zhang and Sejnowski, 2000]. The primate slope of 1.12 is notably lower than that, raising the possibility that as primate brains get larger, a smaller proportion of neurons send axons into white matter. More detailed histological studies have established that the number of glial cells also scales with positive allometry on the number neocortical neurons with an exponent of 1.17 [Herculano-Houzel et al., 2010]. Glial cells include oligodendrocytes, and axon length is proportional to the number of oligodendrocytes [Barres and Raff,1999]. According to the model of Herculano-Houzel et al. [2010], the assumed increase in axons is not sufficient to preserve connectivity among neurons, and the fraction of gray matter neurons that send axons into white matter decreases as gray matter gains neurons. Collectively, these findings suggest that larger primate brains are less well connected than smaller primate brains.

Comparative analyses of the corpus callosum across primate species reach a similar conclusion. Corpus callosum area scales isometrically on brain volume with a slope not significantly different from the expected two thirds for the regression of a surface area on a volume [Rilling and Insel, 1999a], but callosal axon density decreases in larger primate brains [Phillips et al., 2015], implying that interhemispheric connectivity is reduced in larger primate brains. These connections are critical for integrating information from the two cerebral hemispheres [Gazzaniga et al., 1962; Sperry, 1982]. Corpus callosum connections are long, and longer connections are more costly, so perhaps long range connections are preferentially culled as brain size increases. There is some evidence for this within species. In macaque monkeys, long-distance connections between cortical areas are both less common and weaker (i.e., consisting of fewer axons) than shorter connections [Markov et al., 2013]. There is also supportive evidence across species. For example, compared with the smaller mouse brain, macaque monkey brains have proportionally fewer long-distance connections [Horvat et al., 2016].

Not only are long-distance connections sparser and weaker in larger primate brains, they are also expected to be slower because they have to travel longer distances. In principle, this could be offset by increasing axon diameter and myelination. However, when conduction times of corpus callosum axons are estimated based on their length

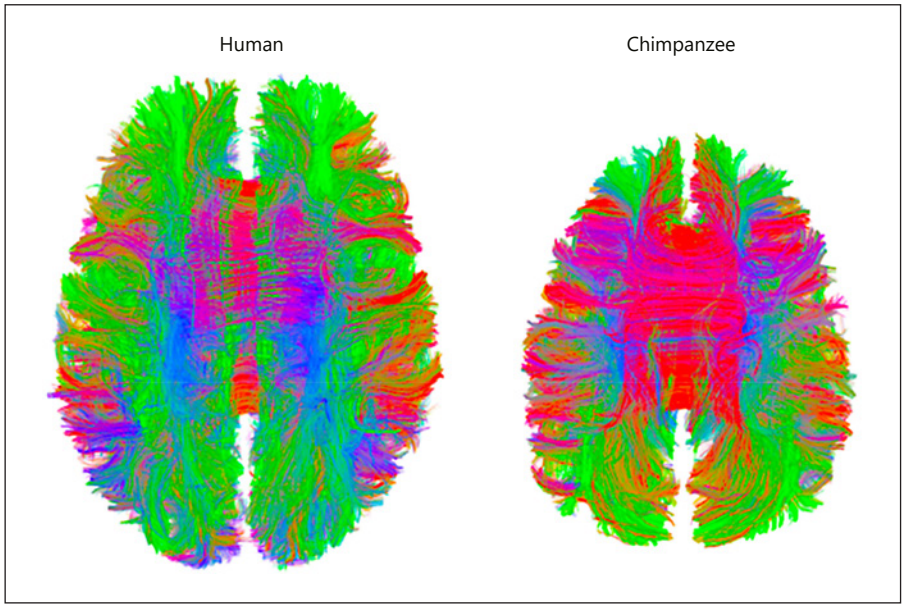

Fig. 2. Example of structural connectome fiber tracking in a human and a chimpanzee brain. Diffusion-weighted imaging is feasible in other species and reveals similarity in the overall fiber architecture between humans and chimpanzees. Red, mediolateral diffusion; blue, dorsoventral diffusion; green, anteroposterior diffusion.

and diameter, conduction times still increase with brain size. Nevertheless, the increase in conduction time with brain size is smaller among the subset of axons in the upper 5% of axon diameters, implying some attenuation of delays by increases in axon diameter [Phillips et al., 2015].

So how do larger primate brains maintain efficiency despite decreases in global connectivity? As suggested earlier, the topological structure – meaning how connections are placed within the network – allows for efficient communication while limiting wiring costs. Both human and macaque connectomes appear to be organized according to small work networks [Modha and Singh 2010; van den Heuvel et al. 2016], at least when focusing the analysis on all but the weakest connections [Markov et al., 2013].

In addition to these allometric effects of brain size on connectivity, humans exhibit some noteworthy departures from allometry. For example, humans appear to have more axons than expected for our cortical neuron number [Herculano-Houzel et al., 2010: Fig. 2C], suggesting that we may tolerate additional costs in service of global network efficiency. Studies have suggested that this increased connectivity may be concentrated in the prefrontal cortex (PFC), as humans have more prefontal white matter than expected for a nonhuman primate of our gray matter volume [Schoenemann et al., 2005; Donahue et al., 2018]. Human PFC is also more gyrified than expected for a nonhuman primate of our brain size [Rilling and Insel, 1999b]. According to one prominent theory, cortical gyri form between strongly connected cortical areas [Van Essen, 1997]. Therefore, the increased gyrification in human PFC may be indicative of increased connectivity of the underlying regions. In addition to the PFC, white matter volume is also larger than expected for a nonhuman primate in the human temporal lobes [Rilling and Seligman, 2002].

Diffusion Tractography

Diffusion tractography allows for the measurement of brain connectivity in vivo and with that comparison of fiber trajectories across species, including humans and chimpanzees. Goulas et al. [2014] defined putative homologous cortical regions in humans and macaque monkeys using a topographically oriented regional map [Kotter and Wanke, 2005] and tracked pathways from each region to every other region in both species. Whereas tract tracer data were used for macaques, diffusion tractography data were used for humans, somewhat limiting a direct comparison of network structure as both methods have their own limitations [van den Heuvel et al., 2016]. Nevertheless, significant overlap in connectivity was found in frontal, temporal and occipital cortex, where overlap is defined as similarity in the connectivity profile of homologous cortical areas in monkeys and humans that is greater than that found between random networks. Less overlap was present in the superior and medial parietal and cingulate cortex. Graph theory metrics were also compared across species, with both species showing high

centrality in the cingulate cortex despite differing patterns of connectivity. In addition, association cortex had the highest centrality and primary cortex had the lowest centrality in both species.

In order to make inferences about human evolution, we need data from chimpanzees in addition to macaque monkeys (Fig. 2). Previously, we explored language-related fiber tracts in humans, chimpanzees, and rhesus macaques. According to Geschwind's classic model of brain language processing: (1) Wernicke's area is involved in speech comprehension, (2) Broca's area is involved in speech production, and (3) the two are linked by a white matter fiber tract known as the arcuate fasciculus [Geschwind, 1970]. Homologues of Wernicke's and Broca's areas have been identified in both macaque monkeys and chimpanzees [Galabdura and Pandya, 1982; Schenker et al., 2010; Spocter et al., 2010]. The macaque arcuate fasciculus has been identified with retrograde tracers [Petrides and Pandya, 2009]. Our group was able to identify the macaque arcuate fasciculus with diffusion tractography. In addition, we were able to compare it with the same pathway in chimpanzees and humans. The human arcuate fasciculus pathway differs from the others in having a prominent projection beyond classic Wernicke's area into the superior temporal sulcus and middle temporal gyrus – cortex known to be involved in syntax and lexical-semantic processing (Fig. 3) [Rilling et al., 2008, 2011; Zaccarella et al., 2017].

The arcuate fasciculus is not the only language-related adaptation of the human connectome. The laryngeal motor cortex (LMC) is a cortical region responsible for voluntary voice production in humans. LMC gives rise to a descending motor pathway that seems to have been rewired to enable speech in humans. Specifically, LMC neurons project directly to brain stem phonatory motoneurons of the nucleus ambiguus in humans but not macaques [Simonyan, 2014].

Diffusion tractography has also been used to compare the "mirror neuron system" in macaques, chimpanzees, and humans. The mirror neuron system is involved in both the observation and execution of actions. It is thought to be involved in simulating observed actions of others that is needed for imitation. The mirror neuron system includes the superior temporal sulcus, which is a visual area that processes biological motion. The superior temporal sulcus provides input into the supramarginal gyrus and inferior frontal cortex, where mirror neurons have been found in macaques [Rizzolatti and Fogassi, 2007]. Dorsal connections of the human mirror neuron system have apparently been enhanced in humans, perhaps to facilitate the spatial and kinematic processing needed to imitate rather than emulate observed actions [Hecht et al., 2013].

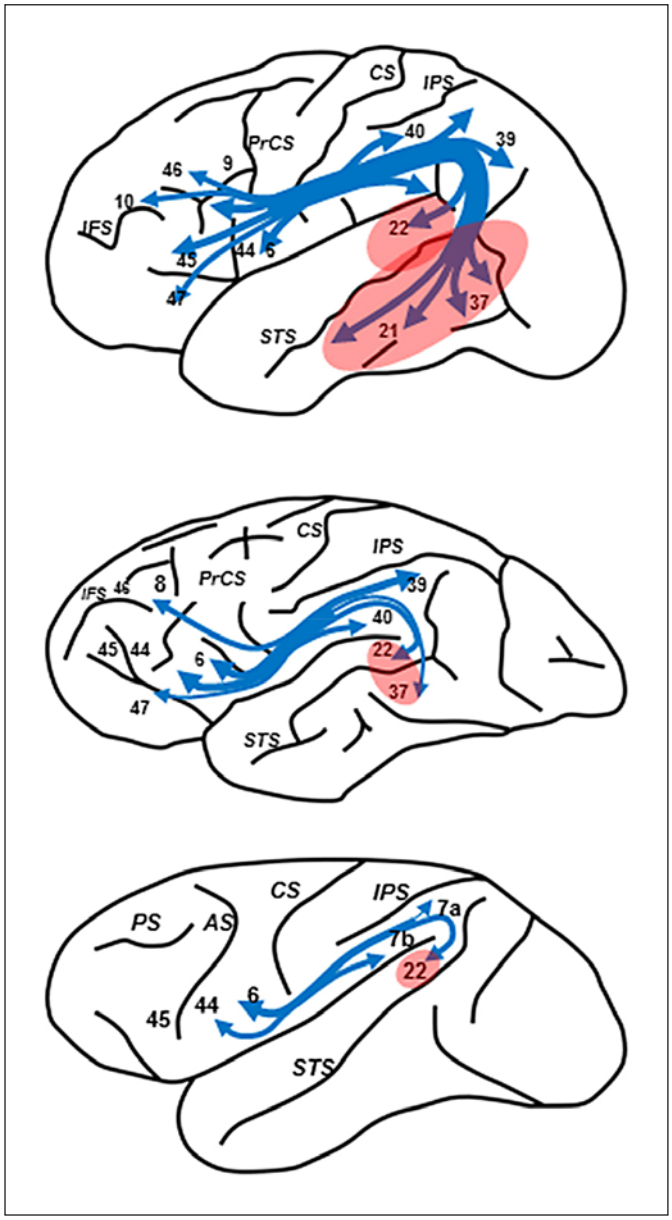

Fig. 3. Schematic illustration of arcuate fasciculus projections in humans (top), chimpanzees (middle), and rhesus macaques (bottom). IFS, inferior frontal sulcus; PrCS, precentral sulcus; CS, central sulcus; IPS, intraparietal sulcus; STS, superior temporal sulcus; PS, principal sulcus; AS, arcuate sulcus. Numerals represent Brodmann areas. Reprinted with permission from Rilling [2017].

Our group has also conducted connectome analyses to identify and compare connectivity hubs in human, chimpanzee, and macaque brains [Li et al., 2013]. For this study,

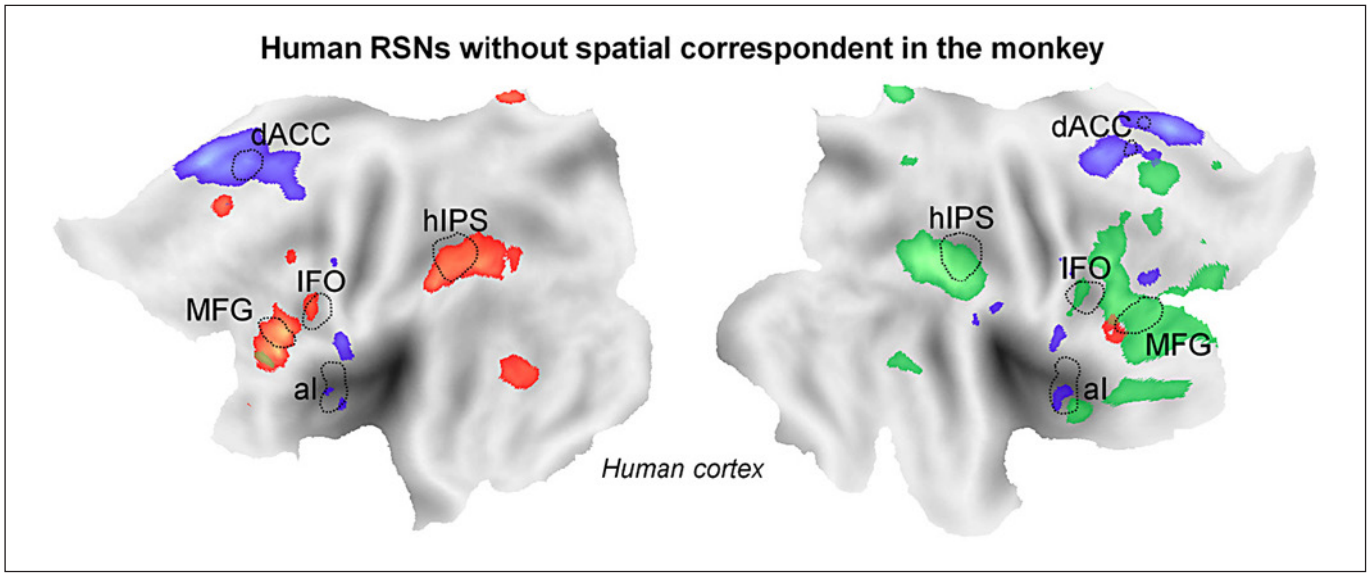

Fig. 4. Resting state functional connectivity networks (RSNs) found in humans but not rhesus macaques. Red, left frontoparietal network; green, right frontoparietal network; blue, bilateral cinguloinsular network; aI, anterior insula; dACC, dorsal anterior cingulate; hIPS, horizontal segment of the intraparietal sulcus; IFO, inferior operculum; MFG, middle frontal gyrus. Reprinted with permission from Mantini et al. [2013].

we used a random parcellation scheme to generate 600 cortical parcels in each species. We then used diffusion tractography to look for connections from each parcel to every other parcel in each species. In attempting to validate the graph theory metrics based on diffusion tractography, we compared our macaque results with those obtained using tracer data. With the known limitations of tractography, agreement was far from perfect, but three regions were identified as hubs using both sets of data: medial PFC (mPFC), medial parietal cortex, and inferior parietal cortex. Among these three regions that were identified as hubs in macaques with both tracer and tractography data, medial parietal cortex was identified as a tractography hub in all three species. On the other hand, both inferior parietal cortex and mPFC were not identified as hubs in all three species. These regions were hubs in macaques and chimpanzees, but not humans. These data suggest potentially significant changes of connectivity patterns within mPFC and inferior parietal cortex during human evolution.

Comparisons of Functional Connectivity

fMRI has been used to compare functional brain connectivity across primate species. One study found widespread similarity in resting state functional connectivity networks between awake humans and awake macaque monkeys [Mantini et al., 2013]. Five sensorimotor and six association cortex networks were identified in both species. However, the "language" network had more extensive temporal lobe involvement in humans, consistent with the earlier suggestion of expanded lexical-semantic cortex in humans. Furthermore, three human-specific networks were identified, including two symmetric frontoparietal networks that the authors speculate may be involved in tool use. The third network involves the dorsal anterior cingulate cortex (ACC) and anterior insula, both of which are critically involved in empathy (Fig. 4) [Lockwood, 2016].

In another comparison of macaque and human functional connectivity, albeit with anesthetized macaques, Neubert et al. [2014] conducted a detailed analysis of ventral frontal cortex connectivity. They identified eleven areas with similar connectivity patterns in both species, but one area that could only be identified in humans. The connectivity pattern of human ventrolateral frontal pole could not be identified in macaques. They also found that area Tpt, part of both human Wernicke's area and its homologue in macaques, was more strongly connected with ventrolateral frontal cortex areas in humans than macaques, again consistent with augmentation of language-related pathways in human evolution. Finally, they showed that humans have stronger intrinsic connectivity

within ventrolateral frontal cortex compared with macaques, consistent with the earlier suggestion of increased structural connectivity in human PFC.

Another study compared network hub topology between human and macaque functional connectomes, also in anesthetized monkeys [Miranda-Dominguez et al., 2014]. Posterior cingulate had high "degree" (a graph theory metric reflecting the number of connections a node has) in both species, consistent with tractography studies. On the other hand, humans had higher connectivity of mPFC and lateral parietal cortex, among other areas. These results contrast with anatomical tractography results showing an absence of mPFC and inferior parietal hubs in humans, and demonstrate that structural and functional connectivity are not measuring the same thing and each has its limitations. As mentioned above, functional connectivity does not directly measure physical connections, but rather reflects a statistical dependency between remote physiological events of brain regions and can thus include multisynaptic connections. Diffusion tractography on the other hand has difficulty reconstructing correct diffusion directions in white matter voxels of complex fiber architecture, limiting the accurate reconstruction of, for example, crossing and kissing fiber bundles.

Comparisons among Nonhuman Primates

While there is great interest in identifying special features of human connectivity, comparative connectomics also has the potential to identify specializations in other species. Chimpanzees and bonobos are particularly interesting for case studies given their recent common ancestry and highly divergent social behaviors. In particular, chimpanzees are more aggressive than bonobos, and bonobos may be more empathic. Using diffusion tractography in postmortem brains, the connection from the ventral ACC to the amygdala was found to be larger in bonobos than in chimpanzees. This pathway may be involved in empathy and the regulation of aggressive impulses [Rilling et al., 2012].

Conclusion

From comparative examinations across primate species we may conclude:

Larger primate brains are less well connected than smaller primate brains, presumably due to the high cost of global wiring in larger brains. However, larger primate brains may be able to maintain efficiency by adopting more globally efficient network configurations. Furthermore, data suggest that humans may tolerate more wiring costs in the prefrontal and temporal lobe regions to enhance efficiency beyond allometric predictions.

Although there is significant overlap in structural connectivity between humans and nonhuman primates, human-specific connections are found in cortical areas involved with language, imitation, and tool use, and human brains lack connectivity hubs in medial prefrontal and inferior parietal areas where nonhuman primates may have more densely connected hub areas.

There is widespread overlap between humans and macaques in resting state functional connectivity. However, studies have again observed a number of human-specific connections in regions involved in language, tool use, and empathy. Human specializations in network topology derived from functional connectivity differ from those found with tractography, perhaps due to methodological limitations or to the inclusion of multisynaptic connections in the former.

Comparative connectomics offers the opportunity to detect specializations of connectivity in other primate species besides humans.

Future Directions

Much of the research on comparative primate connectivity has been focused on just a few species (e.g., humans, chimpanzees, bonobos, and rhesus macaques) that are housed in captive settings. However, primates are a diverse order, which offers the opportunity to compare connectomes as a function of phylogeny, ecology, and social organization – perhaps identifying adaptations to particular social and ecological niches. Anatomical tracer and functional connectivity studies depend on living subjects and are mostly limited in their application to animals living in primate centers or colonies that have easy access to laboratory or neuroimaging facilities. However, diffusion tractography can be conducted on postmortem brains collected at zoos or in the wild that are then transported to neuroimaging facilities. Therefore, diffusion tractography offers the opportunity to collect and compare connectivity across a wide range of primate species. Future comparisons of connectivity will need to address the thorny issue of establishing homologous cortical areas across species and should ideally rely on multiple sources of evidence when doing so (cytoarchitecture, myeloarchitecture, connectivity, cortical thickness, receptor finger-

prints, and gene expression profiles, etc.). Further, improvements in tractography methods are needed to help reduce rates of false-positive and false-negative connections and to increase confidence in results. Most comparative connectomics studies are corticocentric, confining their exploration of connectivity to the cerebral cortex, but comparing subcortical connectivity across species may provide important insights into behavioral differences across species. Finally, it will be important to attempt to establish the functional significance of variation in connectivity profiles by examining how these co-vary with behavior and cognition both across and within species.

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Disclosure Statement

The authors have no conflicts of interest.

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