Revealing Complex Functional Topology Brain Network Correspondences Between Humans and Marmosets

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(Dated: August 18, 2023)

Functional correspondences exist in human and non-human primate brains, but this information is still largely unknown. The topological properties of whole-brain functional connectivity hold great potential for unraveling common and distinct patterns across species. In this study, we employed topology graph brain network analysis and examined the similarities and differences in the brain connectome between humans and marmoset monkeys. The results uncover significant resemblances in functional connectivity patterns throughout the brain, particularly in the prefrontal and visual cortices. In addition, we observed distinct brain connections across humans and marmosets during rest and task states. Generally, humans and marmosets have shared and divergent functional brain connections for spontaneous and specific cognitive brain functions.

PACS numbers: 87.18.Sn, 05.45.Xt, 89.75.Fb

The architecture of the human and non-human brain functional connections is optimized by requirements of energy minimization and efficient information transfer [1, 2]. As a sophisticated, self-organizing, and super-energyless biological neural network, the human brain has different information organization and connectivity compared to other non-human primates, and both species have two primary branches that support this powerful hierarchical computation: structural and functional connectivity. One way to explore these properties across species involves quantifying and elucidating the intricate brain topology because previous work has massively overlooked it.

A fundamental cognitive mechanism and clinical needs drive us to study non-human primate animals to better understand human brain function and related brain disorders because of high-level shared genetics [3]. The great apes share substantial similarities in DNA sequences, with human-to-human sharing 99.9%, chimpanzees 98.2%, gorillas 97.7%, orangutans 96.3%, and monkeys, which include macaques and marmosets, share 93% separately [4]. Then, the following fundamental question remains: Are they similarly intelligent? How do the similarities and differences between humans and marmosets in resting and task states support cognitive processes? This has major implications for understanding intelligence across species and contributing to brain disease treatments [5]. We attempt to answer this question using neurophysics intuitions spanning the domains of statistical mechanics, computational neuroimaging techniques, and specific non-invasive functional magnetic resonance imaging (fMRI) to measure and map brain connections [6].

Considered the marmoset commonly used for preclinical brain disease models because brain-related genes are highly conserved between marmosets and humans [3]. Therefore, investigating the complexities of the brain's functional similarities and differences between humans and marmosets will make it interesting for us to uncover the gaps in cognitive and consciousness functions. The common marmoset monkey (Callithrix jacchus), also known as the white-tufted-ear marmoset, is used to satisfy these research goals [7, 8]. All human and marmoset data sets used in this study are from the Human Connectome Project [9] and Marmoset Brain Mapping Project [10] respectively, which are distributed in compliance with international ethical guidelines.

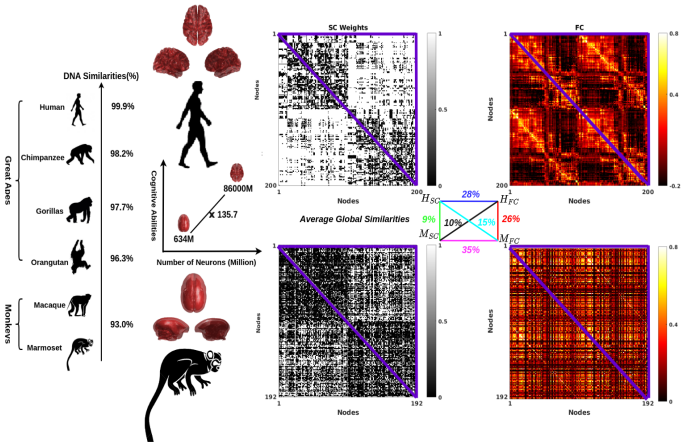

FIG. 1. The humans (H) and marmosets (M) shared similarities and differences in genetics, i.e., DNA sequences, number of neurons, and structural (H_{SC}, M_{SC}) and functional (H_{FC}, M_{FC}) connectivity. From a deeper perspective, the great apes and monkeys have high gene overlap compared to humans, but they have large differences in their number of neurons, i.e., 634M vs. 86000M ($\times$135.7), and their brain structural and functional connections, i.e., 28%, 35%, 9%, 10%, 15% and 26%.

Here, we employed the known cortical networks of the human and marmoset and compared the complex brain topology networks similarities and differences under resting and task states, which has significant implications for our understanding of higher-level cognitive abilities.

Resting states The human and marmoset resting-state connectome data from the Human Connectome Project [9],

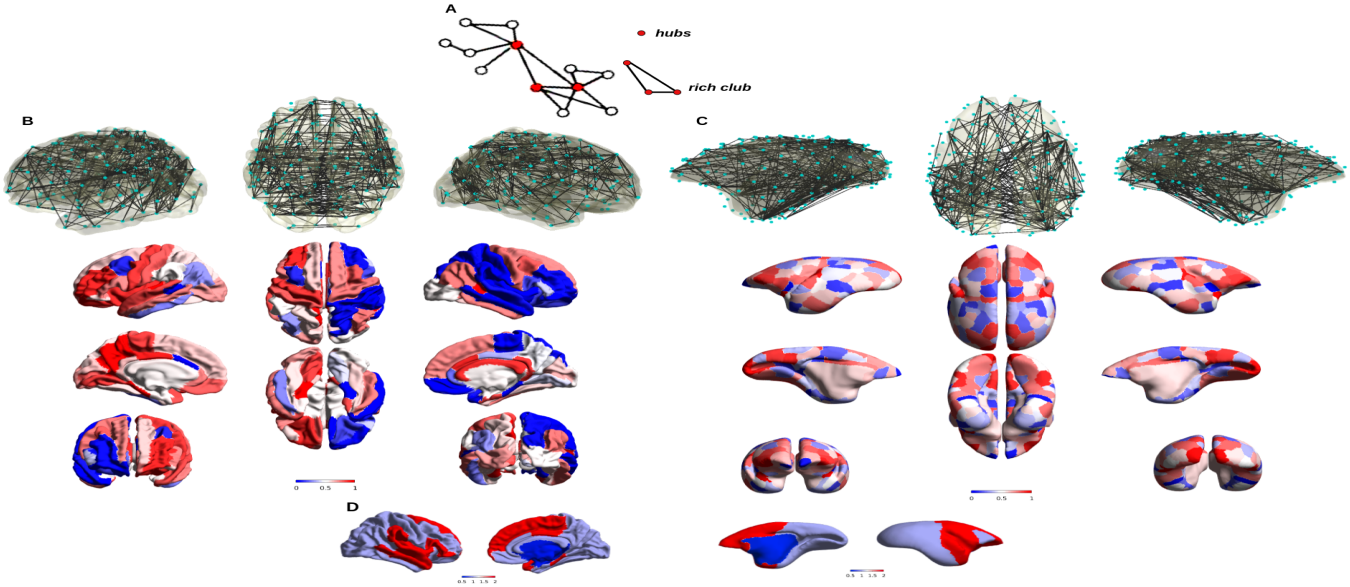

FIG. 2. The topology of functional brain networks mapped to human primate and non-human primate brain surfaces from functional connectivity matrices is shown in Fig. 1. The hubness of human primate and non-human primate brain networks (A) (i.e., the left panel (B) is human brain networks and the right panel (C) is marmoset brain networks) is measured from above topology functional networks, and more red regions indicate stronger connectivity (rich hubness) with other brain regions, and the other way around. The network clustering with clustering number $k = 2$ was applied to both humans and marmosets, as shown in (D). The similarities presented were specific to the prefrontal and visual regions.

which used to map human brain connectivity [11, 12], and the Marmoset Brain Mapping Project [10], which used to map marmoset brain connectivity separately [7, 8]. The human and marmoset structural and functional connections are estimated via Pearson correlation from preprocessed diffusion MRI and fMRI, based on parcellation atlases, i.e., the extracted brain activity from brain regions i and j, can be denoted as $X_i = [x_i(1), \cdots, x_i(t)]$, $X_j = [x_j(1), \cdots, x_j(t)]$, then correlation between brain regions i and j is represented as $r_{ij} = \frac{1}{t-1}\sum_t [z_i(t) \times z_j(t)]$, t is the time length of brain activity, and z refers to z-score value. By repeating this procedure for every pair of brain regions, The connectome matrix was generated with a size of $N \times N$, where N represents the total number of brain regions. Here we will have a $H_{SC}/H_{FC} = 200^2$ and $M_{SC}/M_{FC} = 192^2$ connection matrix for humans and marmosets, as shown in Fig. 1, where H refers to humans and M refers to marmosets.

As we mentioned before, physically structured connections constrain primate brain functional connectivity, and they have a moderate relationship, as shown in Fig. 1. Humans and marmosets have similar mean global Pearson correlations for both structural and functional connectivity, i.e., $corr2(triu(H_{SC}), triu(H_{FC}))$, 28% and $corr2(triu(M^E_{SC}), triu(M^E_{FC}))$, 35%, respectively. However, they share small similarities across species in structural and functional connectivity, i.e., $corr2(triu(H_{SC}), triu(M^E_{FC}))$, 15% and $corr2(triu(M^E_{SC}), triu(H_{FC}))$, 10%, and furthermore, structural and functional connectivity also have small global similarities between two species, i.e., $corr2(triu(H_{SC}), triu(M^E_{SC}))$, 9% and $corr2(triu(H_{FC}), triu(M^E_{FC}))$, 26% separately, where E refers to the expend matrix of the same size as the human connectome matrix. The interpretation for this is that humans and marmosets share large functional connectome similarities, but they still have a large gap, and it may be suggested that humans and marmosets have different spontaneous brain activity in the resting state.

To quantify the difference in the topology of brain networks across species, the degree of centrality was applied to both human and marmoset functional connectivity because it holds valuable information for relating macroscopic brain network organization [13]. Assume that degree centrality has a high value, indicating that brain areas have more connections with other brain regions and that these brain regions have rich hubness qualities because degree centrality primarily counts the total number of connections related to a brain region [14], as shown in Fig. 2A.

The degree of centrality of human and marmoset cortical hubs was computed using unthresholded weighted functional connectivity matrices to identify functional hub regions as shown in Fig. 2B,C (i.e., brain regions with numerous connections). This is accomplished by adding all pairwise functional connectivity values of each region together, and it can be represented mathematically as, $C_D = \sum_j r_{ij}$. As shown in Fig. 2B,C,D, we observe some similarities between human and marmoset resting-state cortical hub distributions, i.e., prefrontal and visual regions. Meanwhile, we may discover alterations to cortical

hubs in other brain regions.

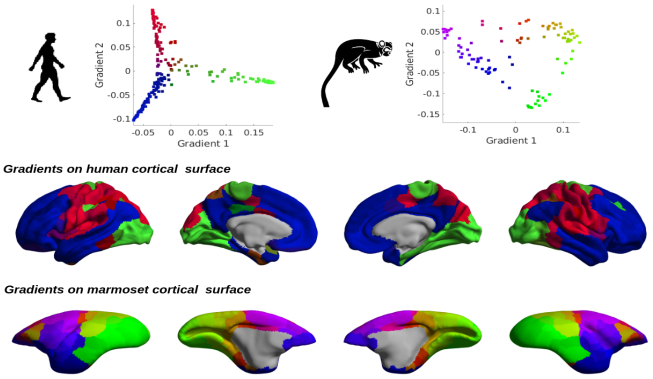

FIG. 3. The functional connection matrices were utilized to generate an affinity matrix, which was then decomposed into a collection of primary eigenvectors describing the axes of greatest variance using linear rotations. The scatter plot displays the scores of each seed on the first two axes (i.e., gradient 1 and gradient 2), with colors representing position in this 2D space, i.e., green refers to visual cortex, red refers to somatosensory and auditory cortex, blue refers to association cortex, and other colors refer to the transfer from a unimodal to a multimodal state. These hues (i.e., gradient 1) can be projected back to the Conte69 hemisphere surfaces of humans [15] and the MBMv4 hemisphere surfaces of marmosets [7] individually.

Recent methodological advances have enabled complex brain properties to be mapped as gradients to low-dimensional representations [16], and these gradients have described the topographical organization of the functional brain connectome from unimodal to transmodal networks. The functional connection matrices were used to compute an affinity matrix that captures the inter-area similarity of a given feature, which was then used to discover a gradual ordering of the input matrix in a lower-dimensional manifold space using dimensionality reduction techniques [17]. As illustrated in Fig. 3, marmosets produce a gradient spectrum pattern for functional connections, and the topographical configuration of functional connections was preserved by the marmoset, which is compatible with humans. Nevertheless, we also see that it has a different gradient spectrum distribution compared with humans. Therefore, the similarities and differences between humans and marmosets are also reflected in the gradient cortical topology network organization. As a result, there is a gradient between the more sensory parts of the cerebral cortex and the more associative ones in humans and marmosets, and we say that human and marmoset brain networks operate on a unimodal and multimodal gradient, respectively, but one way to describe the two ends of this gradient difference is to say that the more sensory end is composed of unimodal areas in the marmoset, whereas the more associative end is composed of multimodal areas.

Task states The functional connectivity "fingerprints" of brain areas to establish similarities between marmosets and humans under task state compared with resting state could be a new way to explore the functional correspondence, because resting state patterns are state agnostic and spontaneous. Therefore, we used movie-driven fMRI to directly compare the visual area activation of marmosets and humans, as well as to establish functional correspondences between visual cortical areas across the visual brain in the two species. The functional movie-driven task fMRI data sets were employed, which recorded neural activity from human and marmoset brain areas under visual stimulus [18]. The similarity matrix was estimated from humans and marmosets neural activity based on Pearson correlation, following the approach used for resting fMRI. As shown in Fig. 4, the similarity matrix includes 26 human brain regions and 25 marmoset brain areas. The maximum co-occurrence brain activity correlation between species can reach 52%, and the mean global co-occurrence brain activity similarity is 0.16/16% but that is small, the median is 0.17, the range is [-0.27, 0.52], and the confidence interval is [0.06, 0.26]. Therefore, compared to the resting state, brain activity increases in the task state, and the increase in functional coupling between species mainly comes from brain visual areas.

In general, we find that these networks are arranged similarly in both species, demonstrating that both higher-order visual areas are mostly conserved in marmoset monkeys and humans. While visual processing is a conserved property between humans and marmoset monkeys, the findings reveal minor, potentially important functional changes. The mean global functional coupling alteration from resting state to task state shows that humans and marmosets share similarities in functional topology organization, but in small amounts, and most structural and functional couplings are different. Therefore, we need to be cautious when we use marmosets as a computational model to compare human high-level cognitive functions, even though both species share high-level genetic overlap and similar structural and functional topology brain functions.

Discussion This letter explained that similarities and differences in brain functions between humans and marmoset monkeys were later commonly used as brain disease models to study brain disease mechanisms. On the one hand, humans and marmosets share large overlaps in genetic sequences, and it's the best choice to model human organisms and related diseases. However, even though they shared large genetic similarities, how about the functional brain connectomes of both species? Throughout this letter, we answer this question by comparing complex brain structural and functional coupling views in both species and following brain network statistical analysis. We show that functional similarities exist in brain functions between humans and marmosets, but they are moderate. There is a large gap in functional brain networks during resting and task states. However, there are some potential limitations that we need to mention here. Firstly, the structural and functional coupling cross-species have moderate global similarities because we directly compare the similarity from the connectivity matrices, this is a rough estimate of correlation across species and may cause

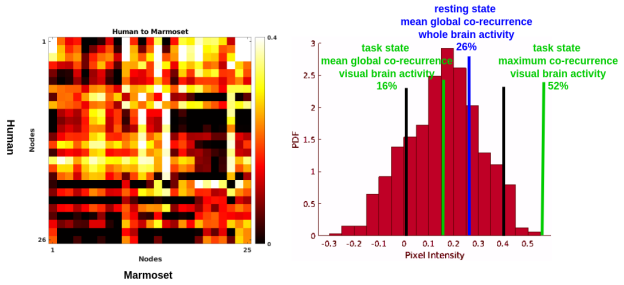

FIG. 4. The functional connectivity similarity matrix between humans and marmosets in response to visual stimuli. In the left panel, lower-order functional connectivity based on pairwise Pearson correlation is presented for 26 human brain areas and 25 marmoset brain regions. The right panel depicts the equivalent probability density distribution (PDF). The two black lines represent the correlation matrix thresholds, while the blue line represents the mean global co-occurrence brain activity similarity between humans and marmosets in resting states (26%) and the two green lines represent the mean global co-occurrence visual brain activity similarity (16%), and maximum co-occurrence visual brain activity similarity (52%) between humans and marmosets in task states.

some deviation, so we need to be cautious. Secondly, all the connections are estimated based on pairwise Pearson correlation, and it will ignore higher-order information organization in the complex brain because we know that brain networks go beyond pairwise interactions [5, 19]. Therefore, it will be a nice future extension work, and we may find some more interesting results. Secondly, we employed graph network analysis, i.e., degree centrality and cortical gradient, to statistically explore the complex topology of brain networks, and the corresponding similarities and differences were indeed found across species, but there are more quantitative metrics that should be considered to fully investigate the properties of brain network information propagating under resting and task states.

Summarizing The presented work shows complex structural and functional topology brain network correspondence between humans and marmosets, and also that structural and functional coupling are basically the same in humans and marmosets, but cross-species structural and functional connectomes are much more distinct. Meanwhile, the functional connections across species also show moderate differences in their resting states. This situation also exists in the task-cognitive state. We also applied network science to quantify the complex brain networks, and we also found that rich hubness and gradient distribution exist in both species, especially in the prefrontal and visual regions. In short, we found that brain function similarities across species exist , but in a moderate part, there is a larger gap in brain function even though both species have high genetic overlap. Therefore, we need to be cautious when we use marmoset monkeys to compare and study intelligent functions with humans.

This work was supported by NSF grant 2112455, and NIH grants R01MH123610 and R01MH119251.

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